II. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based upon the following amendment and remarks are respectfully requested. Claims 29-56 are currently pending and at issue in this application. This response is timely filed with a third-month extension of time.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications. The applicants request entry of the foregoing amendment, as it will either place the application for allowance or place the application in better form for appeal.

Patentability Remarks

Rejection Pursuant the 35 U.S.C. §132, New Matter

In paragraph 6 of the official action, the examiner objected under 35 U.S.C. §132 to the amendment filed August 26, 2005 for allegedly introducing new matter into the disclosure of the invention. Specifically, the examiner asserted that the amendment to SEQ ID NO: 5 and newly submitted Figure 5A requires a declaration. The examiner requests that the declaration attest to the fact that the newly amended sequences are identical to the sequences of the original biological materials deposited with ATCC as identified in the specification. The examiner requests that the verified statement be signed by a person in a position to corroborate these facts.

The applicants submit herewith a declaration pursuant to 37 C.F.R. §1.132, which is executed by Mitchell Reff, PhD. and attests to the fact that the amended 16C10 light chain sequence filed August 28, 2005 is identical to the sequence deposited with the American Type Culture Collection (ATCC Deposit Account No HB-12119 deposited on May 29, 1996). The declaration states that the corrected sequence of the 16C10 light chain antibody is indeed the correct sequence of the 16C10 light chain antibody specifically identified in the application as originally filed. Accordingly, the applicants submit that no new matter has been added to the disclosure through amended SEQ ID NO: 5 and replacement Figure 5A. In view of the foregoing remarks and corroborative declaration, the applicants respectfully

submit that the objection of amended SEQ ID NO:5 and replacement Figure 5A, for allegedly containing new matter, has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §112, First Paragraph

Enablement

In paragraph 5 of the official action, the examiner rejected claims 41 and 55 under 35 U.S.C. §112, first paragraph, as allegedly lacking an enabling disclosure for the claimed invention. Specifically, the examiner asserted that the specification does not describe nor enable any fragment of an anti-CD28 antibody that will bind CD28 treating B cell lymphoma in combination with anti-CD80 antibodies. The examiner alleged that it would be unpredictable to practice the claimed methods of treating B cell lymphoma with combination therapy wherein an antibody fragment lacks antigen specificity.

Amended claims 41 and 55 are directed to the method of claim 29 or 43, wherein said anti-CD80 antibody or CD80-binding fragment thereof is administered in combination with an anti-CD28 antibody or anti-CD28 binding fragment thereof. Support for amended claims 41 and 55 can be found throughout the specification, for example, on page 42, lines 13-18. The applicants submit that the fragments are clearly defined in the amended claims to be anti-CD28 binding fragments to treat B cell lymphoma. The binding specificity of anti-CD28 binding fragments is clearly taught in the specification to be those anti-CD28 antibody fragments that binds to the human CD28 receptor. Production and use of anti-CD28 monoclonal antibody fragments was known to one of skill in the art before the priority date of this application as evidenced by Tan *et al.*, *J. Exp. Med.* 177:165-173 (1993) (Exhibit A). Accordingly, the applicants submit that the specification enables one skilled in the art to make or use the invention of amended claims 41 and 55. In view of the foregoing amendment and remarks, the applicants submit that the rejection of claims 41 and 55 under 35 U.S.C. §112, first paragraph, for lack of enablement, has been overcome and should be withdrawn.

Written Description

In paragraph 7 of the official action, the examiner rejected claims 33-35, 47-49, and 54 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support from the specification. Specifically, the examiner alleged that the specification, as originally filed, does not provide support for the invention of claimed SEQ ID NOS: 2, 5, and

6. The examiner has acknowledged that the nucleotide and amino acid sequence of the ATCC Deposit Accession No. HB-12110 is the same as the sequence filed in the substitute Sequence Listing. However, the examiner requests a verified statement from a person in a position to corroborate the facts set forth in a declaration.

As discussed above, the applicants submit herewith a declaration attesting to the fact that the amended 16C10 light chain sequence filed August 28, 2005 is identical to the sequence deposited with the American Type Culture Collection (ATCC Deposit Account No HB-12119 deposited on May 29, 1996). The declaration further verifies that the amendment to SEQ ID NOS: 2 and 6 (*i.e.*, nucleotide 58 in SEQ ID NO: 2 and nucleotide 523 in SEQ ID NO: 6) were typographical errors and the correct sequence was disclosed in the originally filed Figures 3B (7C10 heavy chain nucleotide and amino acid sequence) and 5B (16C10 heavy chain nucleotide and amino acid sequence) respectively. The declaration of Dr. Reff corroborates that the application as originally filed describes the correct nucleotide and amino acid sequences of 16C10 light and heavy chain antibody and the 7C10 heavy chain antibody. Accordingly, the applicants submit that the originally filed disclosure provides written descriptive support of amended SEQ ID NOS: 2, 5 and 6, and replacement Figure 5A. In view of the foregoing amendment and corroborative declaration, it is believed that the rejection of claims 33-35, 47-49, and 54 under 35 U.S.C. §112, first paragraph, for allegedly lack of proper written descriptive support, has been overcome and should be withdrawn.

Rejection Pursuant to 35 U.S.C. §112, Second Paragraph

In paragraph 7 of the official action, the examiner rejected claims 33-35, 47-49, and 54 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Specifically, the examiner asserted that there is ambiguity concerning the correct sequences associated with the 7C10 and 16C10 antibody. The examiner further alleged that SEQ ID NOS: 2, 5, and 6 are unclear in the absence of a verified statement from a person in a position to corroborate the fact that the newly amended sequences are those sequence derived form the biological materials deposited.

As discussed above, the enclosed declaration of Dr. Reff corroborates the fact that the newly amended sequence of SEQ ID NO: 5 is that sequence derived from the biological materials deposited and that the sequences of amended SEQ ID NO: 2 and 6 correct typographical errors wherein the correct sequences were disclosed in the originally filed figures. In view of the enclosed declaration, the applicants submit that the rejection of claims

33-35, 47-49, and 54 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite, has been overcome and should be withdrawn.

Provisional Rejection—Judicially Created Doctrine of Obviousness Type Double Patenting

In paragraph 8 of the official action, the examiner rejected claims 29-41 and 43-55 under the judicially created doctrine of obviousness type double patenting over claims 23-26, 32, and 37 of co-pending application U.S. Patent Appl. No. 09/758,173, now U.S. Patent No. 6,893,638 (hereafter the '638 patent). The examiner alleged that the claimed inventions of treating patients with B cell lymphoma with the claimed CD80 specific antibodies anticipate each other.

According to 37 C.F.R. §1.130(b), a rejection based upon double-patenting may be overcome in a common ownership situation by filing a terminal disclaimer in compliance with 37 C.F.R. §1.321(c). The applicants assigned their inventorship rights in the present application to Idec Pharmaceuticals Corporation, which thereafter changed its name to Biogen Idec Inc. The assignee also has ownership rights in the allegedly conflicting '638 patent. The applicants shall file a terminal disclaimer when one or more claims is in condition for allowance.

Provisional Rejection under 35 U.S.C. §103(a)

In paragraph 9 of the official action, the examiner asserted that claims 29-41 and 43-55 are directed to an invention that is not patentably distinct from claims 23-26, 32, and 37 of commonly assigned U.S. Patent Appl. No. 09/758,173. The examiner requests that the assignee show under 35 U.S.C. §132 that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter.

Pursuant to 37 C.F.R. §1,78(c), the applicants, through their undersigned attorney, state that the subject matter of claims 23-26, 32, and 37 in U.S. Patent Appl. No. 09/758,173, now U.S. Patent No. 6,893,638 was commonly owned by Idec Pharmaceuticals Corporation at the time the invention was made as directed in claims 29-41 and 43-55 of the instant application. As evidence of the common ownership, enclosed are copies of the assignment recordation sheets for U.S. Patent Appl. No. 09/758,173 and for U.S. Patent Application No. 08/746,361, which is the parent of the instant application (Appendixes B-D).

Specifically, the '173 patent application was a divisional of U.S. Patent Appl. No. 08/487,550 (hereafter the "'550 patent application"), and the ownership rights in the '550 patent application are transferable to the '173 patent application. The assignment for the '550 patent application was assigned to IDEC Pharmaceutical Corporation, as recorded on May 23, 1996, at Reel No. 7832/Frame No. 0646 (Appendix B).

The present application is a continuation of the '361 patent application, and thus ownership rights in the '361 patent application are also had in the present application. The assignment for the '361 patent application was assigned to IDEC Pharmaceutical Corporation, as recorded on January 31, 1997, at Reel No. 8359/Frame No. 0655 (Appendix C). A change of name for both assignments from IDEC Pharmaceuticals Corporation to Biogen Idec Inc. was recorded on August 6, 2004 at Reel No. 015044/Frame No. 0873 (see Appendix D). Accordingly, the subject matter of claims 23-26, 32, and 37 in the '173 patent application was commonly owned by IDEC Pharmaceuticals Corporation (now Biogen Idec Inc.) at the time the invention was made as directed in claims 29-41 and 43-55 of the instant application. In view of the foregoing remarks, the applicants respectfully submit their statement of common ownership satisfies the requirements of 35 U.S.C §132 and thus precludes a rejection under 35 U.S.C. §103(a).

III. CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

By: _____

Thomas A. Cawley, Jr. Ph.D.
Reg. No. 40944
Tel. No. (703) 905-2144
Fax No. (703) 905-2500

TAC/PAJ/wks
P.O. Box 10500
McLean, VA 22102
(703) 905-2000

APPENDIX A

Induction of Alloantigen-specific Hyporesponsiveness in Human T Lymphocytes by Blocking Interaction of CD28 with Its Natural Ligand B7/BB1

By Patrick Tan,* Claudio Anasetti,* John A. Hansen,*‡ Jennifer Melrose,* Mark Brunvand,* Jeff Bradshaw,§ Jeffrey A. Ledbetter,§ and Peter S. Linsley§

*From the *Human Immunogenetics Program, Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104; the ‡Department of Medicine, Division of Oncology, University of Washington, Seattle, Washington 98195; and the §Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121*

Summary

The specificity of T lymphocyte activation is determined by engagement of the T cell receptor (TCR) by peptide/major histocompatibility complexes expressed on the antigen-presenting cell (APC). Lacking costimulation by accessory molecules on the APC, T cell proliferation does not occur and unresponsiveness to subsequent antigenic stimulus is induced. The B7/BB1 receptor on APCs binds CD28 and CTLA-4 on T cells, and provides a costimulus for T cell proliferation. Here, we show that prolonged, specific T cell hyporesponsiveness to antigenic restimulation is achieved by blocking the interaction between CD28 and B7/BB1 in human mixed leukocyte culture (MLC). Secondary T cell proliferative responses to specific alloantigen were inhibited by addition to the primary culture of monovalent Fab fragments of anti-CD28 monoclonal antibody (mAb) 9.3, which block interaction of CD28 with B7/BB1 without activating T cells. Hyporesponsiveness was also induced in MLC by CTLA4Ig, a chimeric immunoglobulin fusion protein incorporating the extracellular domain of CTLA-4 with high binding avidity for B7/BB1. Cells previously primed could also be made hyporesponsive, if exposed to alloantigen in the presence of CTLA4Ig. Maximal hyporesponsiveness was achieved in MLC after 2 d of incubation with CTLA4Ig, and was maintained for at least 27 d after removal of CTLA4Ig. Accumulation of interleukin 2 (IL-2) and interferon γ but not IL-4 mRNA was blocked by CTLA4Ig in T cells stimulated by alloantigen. Antigen-specific responses could be restored by addition of exogenous IL-2 at the time of the secondary stimulation. Addition to primary cultures of the intact bivalent anti-CD28 mAb 9.3, or B7/BB1$^+$ transfected CHO cells or exogenous IL-2, abrogated induction of hyporesponsiveness by CTLA4Ig. These data indicate that interaction of CD28 with B7/BB1 during TCR engagement with antigen is required to maintain T cell competence and that blocking such interaction can result in a state of T cell hyporesponsiveness.

Effective presentation of antigen to T cells requires a complex series of events to initiate the immune response. In addition to processing and presenting antigenic peptides in the context of MHC molecules to specific TCRs, APCs must provide one or more costimulatory signal(s) to fully activate T cells, and induce IL-2 release and DNA synthesis (1–7). In the absence of costimulatory signals, T cells presented with antigen may enter a state of anergy characterized by the failure to activate the IL-2 gene in response to further antigenic stimulation (4). In certain instances, lack of costimulation may lead to activation-driven cell death (8). Binding of surface receptors on T cells to their natural ligands, such as CD2 to LFA-3 (9), CD4 to MHC class II (9), LFA-1 to intercellular adhesion molecule 1 (ICAM-1) or ICAM-2 (10), and CD28 to B7/BB1 (11) have been implicated in facilitating T cell–APC interactions and inducing T cell activation. CD28 signaling stimulates cytokine production by T cells, by regulating gene transcription and also by stabilizing mRNAs (12–16). Binding of CD28 to the B7/BB1 counter receptor costimulates IL-2 mRNA accumulation and T cell proliferation (17–20). CD28-mediated signaling prevents induction of anergy in murine T cell clones (21).

CTLA-4, a molecule homologous to CD28 originally identified by screening of a murine cytolytic T cell cDNA library (22), also binds to B7/BB1 (23). Studies of the binding properties of CTLA-4 and B7/BB1 were facilitated by con-

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struction of a soluble fusion protein consisting of the extracellular domain of CTLA-4 and an IgG γ1 chain (23). CTLA4Ig has a high avidity for the B7/BB1 molecule (K_d ~12 nM) and is a potent inhibitor of immune responses in vitro and in vivo (23–25).

In this study, we have investigated the role of CD28 interactions with B7/BB1 in providing the costimulation necessary to maintain proliferative competence of human T cells. We have found that blocking the interaction of CD28 with B7/BB1 either by anti-CD28 mAb 9.3 Fab fragments or by CTLA4Ig when T cells are presented with alloantigen in a mixed leukocyte culture (MLC)[1] leads to sustained T cell hyporesponsiveness to the specific alloantigen.

Materials and Methods

Ig Fusion Proteins, mAbs, and Transfected Cell Lines. CTLA4Ig was produced by CHO cells transfected with the CTLA4Ig cDNA expression construct and was purified as described previously (23). Purified human mouse chimeric mAb L6 was a gift of Ingegerd and Karl Erik Hellstrom (Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA). Murine mAbs 9.3 (anti-CD28, IgG2a), BB1 (anti-B7/BB1 antigen, IgM), 9E8 (anti-p15E, IgG2a), and T11D7, (anti-Thy1.1, IgM, kind gift of Irwin Bernstein, Fred Hutchinson Cancer Research Center) have been described previously and were purified from ascites before use (26–28). Preparation of Fab fragment of mAb 9.3 has been described previously (29). B7$^+$ CHO cells have been previously described (23) and CD5$^+$ CHO cells were constructed as described (19, 23) using an expressible CD5 cDNA provided by Dr. A. Aruffo (Bristol-Myers Squibb Pharmaceutical Research Institute).

Primary MLC. PBMC were prepared by density gradient centrifugation on Ficoll-Hypaque. The cells were resuspended in medium containing RPMI 1640, 25 mM Hepes, 1 U/ml penicillin, 1 μg/ml streptomycin, and 15% pooled human serum that had been heat inactivated at 56°C for 30 min. As indicated for certain experiments, T cell subsets were purified by negative selection using complement-dependent lysis and panning (30). Responders and stimulators were unrelated individuals chosen so that there was at least one HLA class I and one HLA-DR antigen mismatched within each pair. 5×10^4 responder cells were mixed with 5×10^4 irradiated stimulator cells (3,000 rad) in round-bottomed 96-well plates. These were incubated at 37°C in a 5% CO_2 atmosphere. Assays were performed in triplicate. Cultures were pulsed with one μCi of [^{3}H]thymidine 18 h before harvesting. 10 replicate plates were set up and one was harvested each day for 10 consecutive d. Data are reported as mean cpm of the three replicates. In selected experiments, readings were taken on day 6 of the MLC.

Restimulation Assays. 10^7 PBMC from one individual were primed with an equivalent number of irradiated (3,000 rad) PBMC from another HLA class I- and II-incompatible individual in 25 cm^2 flasks, using identical culture conditions as for primary MLC carried out in 96-well plates. For blocking experiments, cells were cultured for 7 d in the presence of human Ig fusion proteins CTLA4Ig or human–mouse chimeric mAb L6, used as control. Then cells were washed three times, recultured in medium without Ig for an additional 3 d, harvested on day 10, and then restimulated. Primed cells were restimulated with fresh stimulator cells from the original donor or from an unrelated donor. The two donors did not share HLA-DR, DQ, or DP antigens. In experiments of tertiary stimulation, a secondary culture was carried out in flask, as in the first. As indicated in certain experiments, alloantigen-primed CD4$^+$ T cell lines were generated by stimulation with cells from an EBV-transformed B line from an unrelated donor. For the assay, 2×10^4 primed responders and 5×10^4 irradiated stimulators were incubated in 96-well round-bottomed wells in medium without any Ig fusion protein. Assays were performed as detailed for primary MLC.

Generation of CTL. Fresh PBMC or primed cells were tested for CTL precursor activity by priming in MLC. Responder cells (10^7) either fresh or primed as specified for each experiment, and irradiated stimulators (10^7), were cultured for 6 d, harvested, washed twice, and tested for cytolytic effector activity in a 4-h ^{51}Cr-release assay against PHA blasts. Both autologous or stimulator cells were tested as target cells. Maximum and spontaneous release values were obtained by incubating targets with 1% Triton X-100 and medium alone, respectively. Triplicate assays were carried out at E/T ratios of 25:1, 50:1, and 100:1 in V-bottomed 96-well plates. Data are reported as mean percent specific ^{51}Cr-release.

RNA Blot Analysis. RNA was prepared from T cells (~1–3 $\times 10^7$/sample) by a rapid isolation procedure (31). RNA (10 μg) was fractionated on formaldehyde agarose gels, transferred and cross-linked to Zetaprobe membranes (Bio-Rad Laboratories, Cambridge, MA). Probes for IL-2, IL-4, IFN-γ and glyceraldehyde-6-phosphate dehydrogenase (GAPDH) have been previously described (19, 32, 33). DNA fragments were purified and labeled with ^{32}P using a random priming kit (Boehringer Mannheim Corp., Indianapolis, IN). The prehybridized membranes were sequentially hybridized with different ^{32}P-labeled probes. Between hybridizations, each probe was stripped from the blots by boiling in a solution of SSC (0.15 M NaCl, 0.015 M sodium citrate) containing 0.1% SDS.

Results

Induction of Antigen-specific Hyporesponsiveness by Fab Fragments of Anti-CD28 mAb 9.3. Monovalent Fab fragments of the anti-CD28 mAb 9.3 can block T cell proliferative responses to alloantigen in primary MLC, by preventing the interaction of CD28 with its natural ligand B7/BB1 expressed on APCs (12). To evaluate whether there is a long-lasting effect of blocking the CD28 receptor during the initial exposure to antigen, we performed restimulation experiments. Lymphocytes were cultured with alloantigen for 7 d in separate flasks in medium containing 5 μg/ml Fab of 9.3 mAb or control mAb. Cells were then washed to remove mAb, cultured in fresh medium for an additional 3 d, and then restimulated with irradiated PBMC from either the original donor (Fig. 1, *left*) or from a third party donor (Fig. 1, *right*) in medium without mAb. Cells primed in the presence of control mAb and restimulated with PBMC originally used for priming showed a typical accelerated secondary proliferative response peaking on day 3. In contrast, those same primed cells showed a typical primary response, peaking on day 6, when stimulated with PBMC from a third party donor. Cells primed in the presence of 9.3 Fab, however, showed a decreased response when challenged with PBMC from the original donor, yet responded normally to PBMC from a third party donor. These results demonstrate that the secondary proliferative response of human T cells can be inhibited in

[1] *Abbreviations used in this paper:* CTLp, cytolytic precursor; MLC, mixed leukocyte culture.

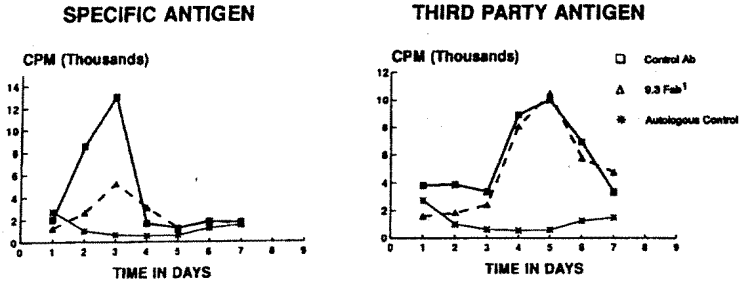

Figure 1. Fab fragments of anti-CD28 mAb 9.3 induce T cell hyporesponsiveness in MLC. For the secondary MLR, responders from a normal individual were primed with cells from an HLA-incompatible donor in the presence of 9.3 mAb Fab (*triangle*) or control (*square*). Cells were restimulated from the original donor (*left*) or a third party donor (*right*) in the absence of mAb. Cells primed in the absence of mAb were restimulated against autologous cells to define the background for the assay (*).

an antigen-specific manner by blocking CD28 during the primary exposure to alloantigen.

Inhibition of T Cell Responses to Alloantigen by CTLA4Ig. To determine whether antigen-specific hyporesponsiveness could also be induced by blocking B7/BB1, the natural ligand for CD28 expressed on APC, further experiments evaluated the activity of CTLA4Ig, a fusion protein with high affinity for B7/BB1. Both responder and irradiated stimulator cells were preincubated with CTLA4Ig or control Ig for 30 min at 37°C before mixing. CTLA4Ig inhibited primary alloproliferative responses by 50–85%, and maximal inhibition was seen at or above 2.5 μg/ml of CTLA4Ig (data not shown), consistent with previous findings (23). mAb BB1 (26), a murine IgM antibody that binds to the B7/BB1 antigen with lower avidity than CTLA4Ig (23) inhibited MLR by only ~30%. Thus, CTLA4Ig inhibited primary T cell responses more efficiently than mAb BB1, although the inhibition achieved was not complete.

Previous studies had shown that $CD4^+/CD28^+$ T cells constitute 95–99.5% of $CD4^+$ peripheral blood T cells and proliferate vigorously to HLA class II determinants in MLR (34), whereas $CD4^+/CD28^-$ T cells constitute 0.5–5.0% of all $CD4^+$ T cells and respond poorly in MLR (35), and $CD8^+$ T cells do not proliferate at all in human MLR. By flow microfluorimetric analysis we found that $CD4^+$ cells constituted 79% of viable lymphocytes on day 6 of an MLR carried out in the presence of control Ig compared with 56% in the presence of CTLA4Ig, and $CD28^+$ cells constituted 72% of viable lymphocytes after an MLR carried out in the presence of control Ig compared with 56% in the presence of CTLA4Ig. Thus, CTLA4Ig blocked the increase in the proportion of $CD4^+$ and $CD28^+$ cells during MLR. Since requirements for proliferation are more stringent in naive than in memory cells, one expected MLR response of naive cells to be more susceptible to inhibition by CTLA4Ig than MLR response of memory cells. $CD4^+/CD45RA^+$ (naive) and $CD4^+/CD45RO^+$ (memory) T cell subsets were purified by negative selection, through panning of PBMC obtained from adult volunteers, and tested in MLR. CTLA4Ig inhibited thymidine uptake of $CD4^+/CD45RA^+$ cells by 84% and $CD4^+/CD45RO^+$ cells by 74%. As an alternative source of naive T cells, mononuclear cells were obtained from umbilical cord blood and tested in MLR. CTLA4Ig inhibited thymidine uptake of cord blood cells stimulated by irradiated PBMC obtained from an unrelated adult by 78%. These results indicate that CTLA4Ig can inhibit proliferative responses to HLA class II determinants in either naive or memory T cells with the $CD4^+$ and $CD28^+$ phenotype. However, in no T cell subset analyzed was the inhibition complete.

Effect of CTLA4Ig on Lymphokine Production. Proliferative T cell responses to alloantigen occurring despite the presence of CTLA4Ig might not be driven by IL-2, but rather by IL-4. Steady state message for IL-2, IL-4, and IFN-γ was measured in mRNA prepared from proliferative $CD4^+$ T cell lines stimulated by specific alloantigen in the presence or absence of CTLA4Ig (Fig. 2). Transcripts for IL-2 and IFN-γ were lower in mRNA from cells cultured with CTLA4Ig compared with control cells. In contrast, transcripts for IL-4 peaked at 4 h after stimulation and were detected at similar levels in mRNA from cells cultured with or without CTLA4Ig. Thus, IL-2 and IFN-γ transcripts do not accumulate in T cells stimulated by alloantigen when B7/BB1 is blocked by CTLA4Ig, whereas IL-4 transcripts do accumulate. Therefore, IL-4 could drive antigen-specific T cell proliferation which occurs despite blocking by CTLA4Ig.

Induction of Antigen-specific Hyporesponsiveness by CTLA4Ig. To evaluate the effect of CTLA4Ig on secondary responses,

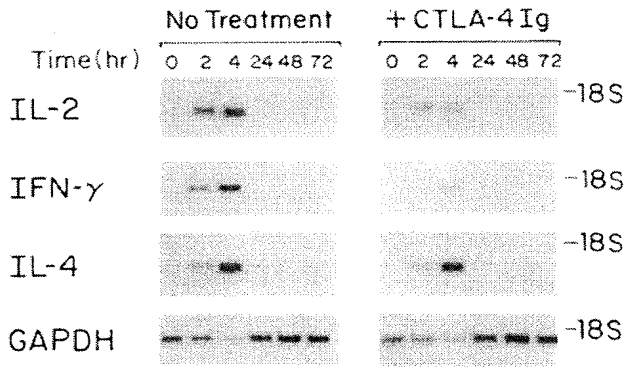

Figure 2. Regulation of lymphokine transcripts by CTLA4Ig. Resting alloantigen-primed $CD4^+$ T cells (2×10^7) were collected and restimulated with irradiated lymphoblastoid cells. Cells were harvested at the indicated times, RNA was extracted and analyzed by blot analysis. The blot was sequentially hybridized with ^{32}P-labeled probes for IL-2, IL-4, IFN-γ and GAPDH, as described in Material and Methods. Migration positions are noted of the 28S and 18S ribosomal RNA species visualized by ethidium bromide staining.

lymphocytes were cultured with alloantigen for 7 d in medium containing 5 μg/ml CTLA4Ig or control Ig. Cells were then washed to remove Ig, cultured in fresh medium for an additional 3 d, and then restimulated with irradiated PBMC from either the original donor (Fig. 3, *top left*) or from a third party donor (Fig. 3, *bottom left*) in medium without Ig. Cells primed in the presence of CTLA4Ig showed a decreased response when challenged with PBMC from the original donor, yet responded normally to PBMC from a third party donor. Flow microfluorimetric analysis of $CD4^+$ cells on day 3 of the secondary cultures indicated that expression of the IL-2 receptor α chain (CD25) was lower in CTLA4Ig-treated cultures than in controls (data not shown). Antigen-specific hyporesponsiveness was achieved with as low as 1 μg/ml of CTLA4Ig in the priming culture, but there was no effect on responsiveness to third party donors even at a CTLA4Ig concentration of 10 μg/ml (data not shown). Hyporesponsiveness was demonstrated in cells cultured with alloantigen in the presence of CTLA4Ig for 7 d, and then rested in medium alone for 20 d and 27 d after initiation of the culture (Fig. 3). In six experiments using different pairs of responder and stimulator cells, primary MLC in the presence of CTLA4Ig inhibited the secondary proliferative responses to the specific alloantigens by an average (±SD) of 70 ± 13%, whereas responses to third party donors were unaffected (4 ± 3% inhibition). Secondary proliferative responses to specific alloantigen were inhibited by an identical degree, if the primary cultures were carried out in the presence of either CTLA4Ig (84% inhibition) or anti-CD28 mAb Fab (83% inhibition), but no greater inhibition was achieved by a combination of the two (84% inhibition). These results demonstrate that secondary proliferative responses can be specifically inhibited by primary exposure of T cells to alloantigen in the presence of either anti-CD28 mAb Fab fragments or CTLA4Ig, and are consistent with the model that both agents block the same pathway of T cell activation.

Effect of CTLA4Ig on Responsiveness of Primed Cells. Further experiments were designed to determine whether alloantigen-specific hyporesponsiveness could be induced by CTLA4Ig in primed cells. Cells were primed to alloantigen in medium without CTLA4Ig or control for 10 d (Fig. 4, *top left*). Cells were then washed and restimulated with irradiated cells from the original donor. Both responder and stimulator cells were incubated with CTLA4Ig or control Ig for 30 min at 37°C before mixing. The secondary proliferative response was inhibited by CTLA4Ig compared with the Ig control (Fig. 4, *top right*). In separate cultures set up in flasks, primed cells were restimulated with PBMC from the original donor in the presence of CTLA4Ig or control Ig for 7 d, washed to remove the Ig, and rested in medium for

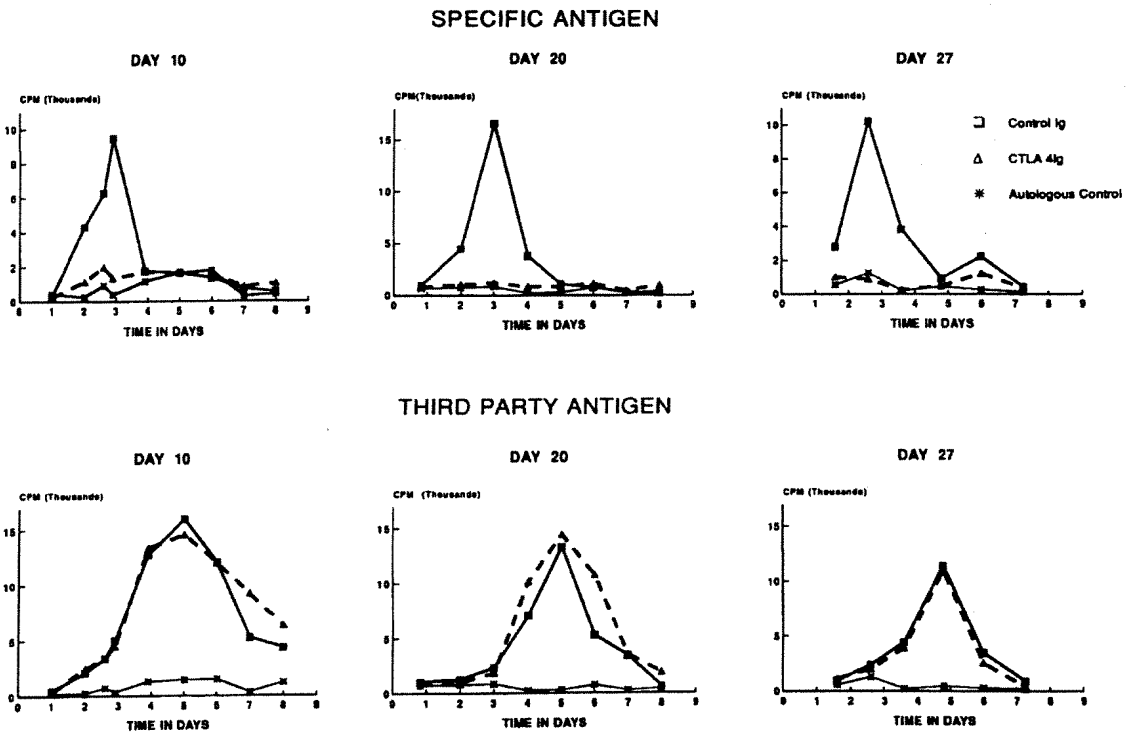

Figure 3. CTLA4Ig induces antigen-specific hyporesponsiveness in unprimed cells. Responders from a normal individual were primed with cells from an HLA-incompatible donor in the presence of CTLA4Ig (*triangle*) or control Ig (*square*). At the indicated time points, primed cells were restimulated from the original donor (*top*) or a third party donor (*bottom*) in the absence of Ig. Cells primed in the absence of Ig were restimulated against autologous cells to define the background for the assay (*).

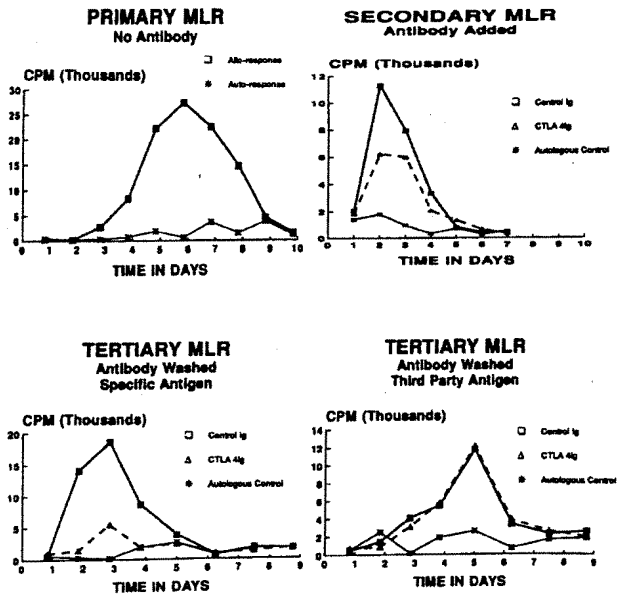

Figure 4. CTLA4Ig induces antigen-specific hyporesponsiveness in primed cells. PBMC were primed with allogeneic stimulators (*square*) in absence of Ig (*top left*; [*] autologous stimulation). Primed cells were restimulated in secondary MLR with cells from the original donor (*top right*) in the presence of CTLA4Ig (*triangle*) or control Ig (*square*). Cells from the respective cultures were washed and then restimulated in a tertiary MLR (*bottom*) with cells from the original donor (*left*) or a third party donor (*right*) in absence of Ig. Cells primed in the absence of Ig were restimulated against autologous cells to define the background for the assay (*).

an additional 3 d. They were then stimulated again in a tertiary culture with specific or third party alloantigen. Cells preincubated with control Ig exhibit a typical anamnestic response when restimulated with cells from the original donor. In contrast, cells preincubated with CTLA4Ig showed a diminished response to cells from the original donor (Fig. 4, *bottom left*), whereas their response to a third party donor was unaffected (Fig. 4, *bottom right*). These findings indicate that primed cells can also become hyporesponsive if exposed to alloantigen in the presence of CTLA4Ig.

Kinetics of Induction of Hyporesponsiveness by CTLA4Ig. To determine the duration of exposure to CTLA4Ig necessary for development of hyporesponsiveness, cells were washed on days 1, 2, or 3 of primary MLC, resuspended in fresh medium without Ig, and rested until day 10 when they were restimulated with irradiated PBMC from the original donor or from a third party donor. Primary MLC in the presence of CTLA4Ig for 2 or 3 d inhibited the secondary response to the original donor >80%, but had no effect on the response to third party donors. Primary MLC in the presence of CTLA4Ig for 1 d inhibited the secondary response to the original donor by only ~15%. Therefore, maximum induction of antigen-specific hyporesponsiveness is achieved in MLC after 2 d of incubation with CTLA4Ig.

Effect of IL-2 on Hyporesponsive Cells. Hyporesponsiveness in secondary MLR could be due to the death of antigen-specific T cells occurring during the primary culture or to the acquisition of a defect in one of the cellular functions that limits the rate of cell proliferation, such as IL-2 production. Addition of exogenous IL-2 to secondary cultures could help determine whether IL-2-responsive, antigen-specific T cells were still alive. Primary MLCs were set up in medium containing CTLA4Ig or control Ig. When challenged with PBMC from the original donor, cells primed in the presence of CTLA4Ig showed a lower response (Fig. 5, *center*) than cells primed in the presence of control Ig (Fig. 5, *left*), yet responded equally well to PBMC from a third party donor. Exogenous rIL-2 added at 10 IU/ml to secondary cultures restored responsiveness to specific alloantigen of cells primed in the presence of CTLA4Ig (Fig. 5, *right*). These results indicate that presentation of antigen while blocking interaction of CD28 with B7/BB1 can induce a state of T cell hyporesponsiveness to antigen which can be corrected by exogenous IL-2.

Effect of IL-2 on Induction of Antigen-specific Hyporesponsiveness by CTLA4Ig. CD28 signaling concurrent with TCR engagement results in IL-2 secretion, T cell activation and proliferation. Therefore, we tested whether exogenous IL-2 could provide T cells with a signal that could bypass the block provided by CTLA4Ig in the primary MLC and prevent induction of antigen-specific hyporesponsiveness. Primary MLCs were set up with CTLA4Ig, with or without rIL-2 at 10 IU/ml

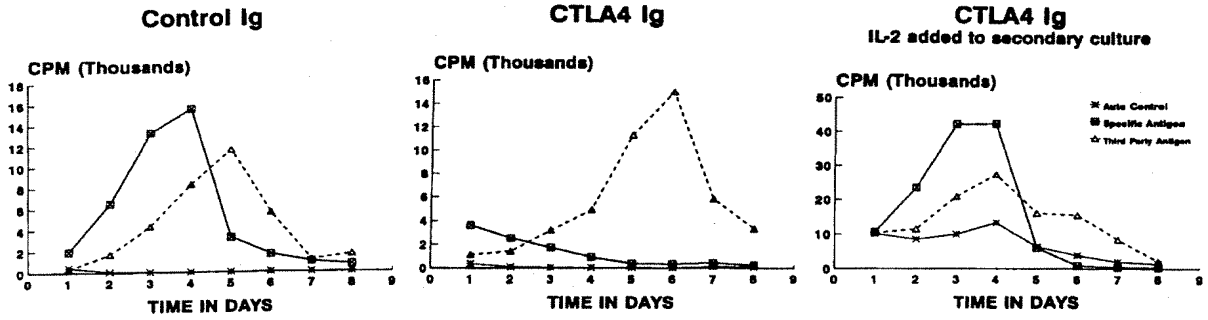

Figure 5. Exogenous IL-2 restore responsiveness to specific antigen. Cells were primed to alloantigen in the presence of control Ig (*left*) or CTLA4Ig (*center* and *right*). Primed cells were restimulated with autologous cells (*), cells from the original donor (*square*) or a third party donor (*triangle*) in the absence of Ig. Cells primed in the presence of CTLA4Ig were restimulated in medium (*center*) or 10 μ rIL-2 (*right*).

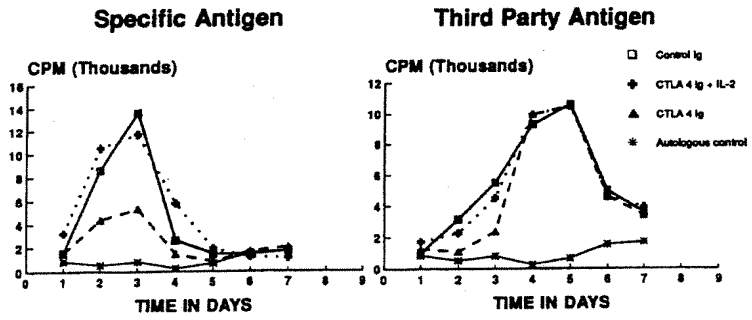

Figure 6. Exogenous IL-2 prevents induction of antigen-specific hyporesponsiveness by CTLA4Ig. Cells were primed in the presence of CTLA4Ig (*triangle*), or control Ig (*square*), or CTLA4Ig plus IL-2 (*cross*). Primed cells were restimulated with cells form the original donor (*left*) or a third party donor (*right*) in the absence of Ig or IL-2. Cells primed in the absence of Ig were restimulated against autologous cells to define the background for the assay (*).

added at the initiation of the culture or control Ig. Cells primed in the presence of CTLA4Ig alone showed hyporesponsiveness when restimulated with the specific alloantigen (Fig. 6, *left*). However, cells primed in the presence of CTLA4Ig plus rIL-2 showed the same degree of secondary response to the specific stimulators as cells primed in the presence of control Ig. Neither CTLA4Ig nor rIL-2 affected secondary responses to cells from third party donors (Fig. 6, *right*). These results indicate that antigen-specific hyporesponsiveness induced by priming T cells in the presence of CTLA4Ig in MLC can be prevented by stimulation with exogenous IL-2.

Effect of Anti-CD28 mAb 9.3 or Cell-bound B7/BB1 Receptor on Induction of Antigen-specific Hyporesponsiveness by CTLA4Ig. In contrast to monovalent Fab fragments of anti-CD28 mAb 9.3, the bivalent intact mAb 9.3 can crosslink CD28 molecules and activate T cells efficiently (29). Therefore, we tested whether the intact mAb 9.3 could deliver a signal to T cells and prevent induction of hyporesponsiveness by CTLA4Ig. Primary MLCs were set up with CTLA4Ig with or without mAb 9.3 or controls. Cells primed in the presence of CTLA4Ig alone showed hyporesponsiveness, compared with cells primed in the presence of control Ig alone (not shown) or control Ig plus mAb 9.3, when restimulated with the specific alloantigen (Fig. 7, *left*). However, cells primed in the presence of CTLA4Ig plus mAb 9.3 showed the same degree of secondary response to the specific stimulators as was shown by cells primed in the presence of control Ig and mAb 9.3. Neither CTLA4Ig nor mAb 9.3 affected secondary responses to cells from third party donors (Fig. 7, *right*).

Further experiments tested the effect of exogenous B7/BB1 antigen expressed on transfected CHO cells. Irradiated (10^4 rad) $B7^+$ CHO cells (19) were mixed with fresh responder PBMC at a ratio of 1:100, before addition of CTLA4Ig or control Ig and irradiated stimulator PBMC. MLC without CHO cells but with CTLA4Ig or control Ig alone were set up in parallel. Cells primed in the presence of CTLA4Ig alone showed hyporesponsiveness to specific alloantigen when compared with cells primed in the presence of control Ig. Cells primed in the presence of CTLA4Ig and the negative control $CD5^+$ CHO cells also showed hyporesponsiveness. In contrast, cells primed in the presence of CTLA4Ig and $B7^+$ CHO cells showed the same degree of secondary response to the specific stimulators, as was shown by cells primed in the presence of control Ig and no CTLA4Ig (data not shown). Neither CTLA4Ig nor transfected CHO cells affected secondary responses to cells from third party donors (data not shown). These results indicate that antigen-specific hyporesponsiveness induced by priming T cells in the presence of CTLA4Ig in MLC can be prevented by stimulating CD28 with mAb 9.3 or with the natural ligand B7/BB1.

Effect of CTLA4Ig on CTL Generation. CTLA4Ig did not inhibit the effector phase of the cytolytic reaction by activated CTL against allogeneic target T cell blasts (data not shown). To determine whether CTLA4Ig added to the primary MLC could block the generation of CTL activity, MLCs were set up in medium containing CTLA4Ig or control Ig for 5 d. Cells primed in the presence of CTLA4Ig showed a fourfold decrease in cytolytic activity against allogeneic target T cell blasts when compared with cells primed in the presence of control Ig (data not shown). To determine whether the block in the generation of CTL activity by CTLA4Ig was specific, MLCs were set up in medium containing

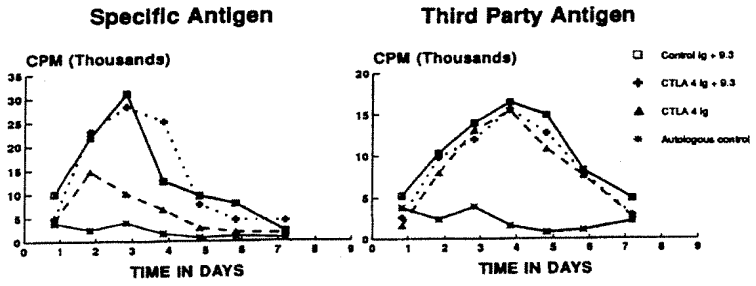

Figure 7. Intact mAb 9.3 blocks induction of antigen-specific hyporesponsiveness by CTLA4Ig. Cells were primed in the presence of CTLA4Ig (*triangle*), or control Ig plus mAb 9.3 (*square*), or CTLA4Ig plus mAb 9.3 (*cross*). Primed lymphocytes were restimulated with cells from the original donor (*left*) or a third party donor (*right*) in the absence of Ig. Cells primed in the absence of Ig were restimulated against autologous cells to define the background for the assay (*). This experiment is representative of two other experiments of similar design that achieved identical results.

CTLA4Ig or control Ig for 7 d. Cells were washed and recultured in fresh medium without CTLA4Ig for 3 d. Cells were then restimulated with irradiated PBMC from the original donor or from a third party donor for 3 d and then tested for cytolytic activity. Cells previously primed in the presence of CTLA4Ig again showed a fourfold decrease in cytolytic activity against specific alloantigen (Fig. 8, *left*) when compared with cells primed in the presence of control Ig. In contrast, cells previously cultured in the presence of CTLA4Ig were able to generate cytotoxic activity against a third party donor to the same degree as cells cultured with control Ig (Fig. 8, *right*). Thus, CTLA4Ig inhibited the generation of specific CTL.

Discussion

Our study demonstrates that long-lasting, antigen-specific hyporesponsiveness can be induced in T cells by exposure to alloantigen while blocking the interaction of CD28 on T cells with B7/BB1 on allogeneic APC. Effective blockade could be achieved using either monovalent anti-CD28 mAb 9.3 fragments or CTLA4Ig, a soluble recombinant fusion product of human CTLA-4 and IgG γ1 chain, the binds to B7/BB1 with high avidity. Previous reports had shown that anti-CD28 mAbs augment proliferation of human T cells in the presence of specific antigen and defective APCs (16). Further work showed that interaction of CD28 with B7/BB1 provides a costimulatory signal for T cell activation (17–20). Data from Schwartz and other investigators (4–7, 36) indicated that in the absence of costimulatory signals provided by the APC, T cells encountering specific antigen enter a state of anergy characterized by an IL-2 production defect. Harding et al. (21) demonstrated that CD28 signaling can prevent anergy in murine T cell clones. Our data are consistent with the model that the CD28–B7/BB1 interaction can provide a costimulus required for T cell activation. CD28 ligation is required for IL-2 gene activation in antigen-specific responses. Blocking CD28 ligation by either 9.3 mAb Fab or CTLA4Ig may inhibit IL-2 expression and elicit a state of T cell hyporesponsiveness.

Human MLR experiments allowed us to study the requirements for antigen-specific responses of $CD4^+/CD28^+$ cells, since proliferation of $CD4^+/CD28^-$ cells and $CD8^+$ cells cannot be detected in this model system. CTLA4Ig blocked proliferation of $CD4^+/CD28^+$ in primary MLC and achieved a similar degree of inhibition in naive and memory T cells. A state of antigen-specific hyporesponsiveness could be induced by CTLA4Ig in primed as well as in unprimed cells. Secondary proliferative responses to the specific alloantigen were decreased, but not abolished by the presence of either anti-CD28 mAb 9.3 Fab or CTLA4Ig in primary cultures. Residual T cell responsiveness hardly could be explained by incomplete blocking of the CD28 or B7/BB1 receptors, since anti-CD28 mAb Fab and CTLA4Ig used together did not demonstrate additive inhibitory activity. T cell proliferation could be induced through CD28-independent activation pathways initiated by other accessory receptors, such as ICAM-1 (10). The heat-stable antigen also functions as a costimulatory molecule and regulates T cell responsiveness (37). CTLA4Ig blocked antigen-mediated activation of IL-2 and IFN-γ expression, but did not block IL-4 expression. Thus, IL-4 might be responsible for driving T cell proliferation in primary or secondary MLR. Further experiments will need to address whether neutralization of IL-4 in culture can achieve complete T cell unresponsiveness in this model.

Exogenous IL-2 could restore antigen-specific proliferative responses in secondary cultures, suggesting that hyporesponsiveness was not the result of T cell death but, instead, was likely the result of an acquired T cell defect in IL-2 production. Whether blocking alloantigen-mediated T cell activation by CTLA4Ig can induce a sustained defect in IL-2 production remains to be verified. Exogenous IL-2 added at the beginning of the primary MLC prevented induction of antigen-specific hyporesponsiveness by CTLA4Ig in this study. This finding contrasts with the observation in the model using murine T cell clones stimulated in absence of accessory cells, where exogenous IL-2 cannot prevent hyporesponsiveness. As opposed to the murine model, MLR cultures contain accessory cells and with them an indefinite number of stimuli that could make less stringent the requirements for T cell activation.

Both CD28 and CTLA-4 are natural ligands for B7/BB1, a receptor expressed on activated B lymphocytes and other APCs (38–41). Once expressed, B7/BB1 interacts with CD28 and CTLA-4 to provide a stimulus for T cell activation (18, 42). The time required for B7 expression, 16–24 h after B cell activation (39), can explain why T cell hyporesponsive-

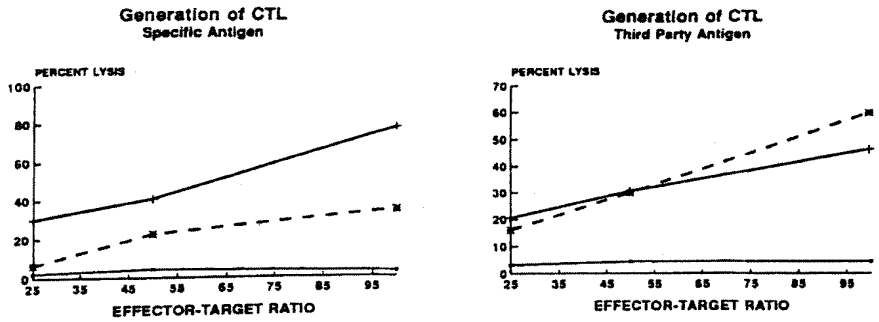

Figure 8. CTLA4Ig inhibits CTL generation. Responder cells were primed in the presence of CTLA4Ig (*) or control Ig (*cross*). Primed cells were restimulated with cells from the original donor (*left*) or from a third party donor (*right*) in the absence of Ig and cytotoxic activity was assayed on day 3 of the secondary cultures against PHA stimulated T lymphoblasts from the respective donors. Lysis of autologous targets (*square*) by cells primed in absence of Ig define the background for the assay. This experiment is representative of two other experiments of similar design that achieved identical results.

ness is not completely achieved in MLC by 24 h but requires 48 h of incubation with CTLA4Ig. CD28 ligation by the whole anti-CD28 mAb 9.3 could prevent induction of hyporesponsiveness by CTLA4Ig in MLC. Hyporesponsiveness was also prevented by mixing irradiated $B7^+$ CHO cells with responder lymphocytes at the initiation of the MLC before adding CTLA4Ig. Prevention of hyporesponsiveness by $B7^+$ CHO cells may be achieved by direct stimulation of T cells through CD28 or by neutralization of soluble CTLA4Ig. We favor the former hypothesis since $B7^+$CHO cells were used at a very low frequency in the culture (1:100:100, $B7^+$ CHO cells/responders/stimulators). Under these experimental conditions, we calculated that the concentration of CTLA4Ig in the culture exceeded the concentration of the B7/BB1 receptor on the surface of CHO cells by at least 100-fold on a molar basis. Thus, it was unlikely that CTLA4Ig could be neutralized by $B7^+$ CHO cells. The role of the CTLA-4 receptor in the achievement of T cell hyporesponsiveness has not been addressed directly in our studies. However, since blocking CD28 by 9.3 mAb Fabs induced a level of hyporesponsiveness comparable to blocking B7/BB1 by CTLA4Ig, and since triggering CD28 by the intact 9.3 mAb could completely overcome hyporesponsiveness induced by CTLA4Ig, it is unlikely that signaling by CTLA-4 per se is of major importance in regulating T cell responses.

CTLA4Ig not only blocked primary and secondary proliferative responses but also blocked activation of cytolytic precursors (CTLp). Cells exposed to alloantigen in the presence of CTLA4Ig were found to generate markedly diminished specific cytolytic activity. These results suggest that generation of cytolytic activity in the primary culture in the presence of CTLA4Ig was an unlikely explanation for the hyporesponsiveness in secondary culture. Recent findings indicate that CD28 interaction with B7/BB1 can amplify T cell–mediated cytolysis at the effector phase (43). In our experiments, however, there was no interference of CTLA4Ig at the lytic stage, probably because activated T cell targets do not express B7/BB1. It remains to be determined whether CTLA4Ig blocked CTLp activation directly or indirectly by inhibiting Th cell functions.

Defining the role of the interaction between CD28 and B7/BB1 and between other T cell accessory receptors and their natural ligands will help understand the mechanisms for self-tolerance, propose new strategies to manipulate the immune response, and achieve transplantation tolerance (24, 25, 44).

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Address correspondence to Claudio Anasetti, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

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APPENDIX B

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Patent Assignment Abstract of Title

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Publication #: US20010024648 **Pub Dt:** 09/27/2001

Inventors: Darrell R. Anderson, Peter Brams, Nabil Hanna, William S. Shestowsky, Cheryl Heard

Title: METHODS FOR TREATING B CELL LYMPHOMA USING CD80-SPECIFIC ANTIBODIES

Assignment: 1

Reel/Frame: 015044/0873 **Recorded:** 08/06/2004 **Pages:** 7

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Assignor: IDEC PHARMACEUTICALS CORPORATION **Exec Dt:** 11/12/2003

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3030 CALLAN ROAD
SAN DIEGO, CALIFORNIA 92121

Correspondent: PILLSBURY WINTHROP LLP
THOMAS A. CAWLEY, JR.
P.O. BOX 10500
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ALEXANDRIA, VA 22313-1404

100181709A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 05/23/1996

REEL/FRAME: 7832/0646
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ANDERSON, DARRELL R.

DOC DATE: 11/13/1995

ASSIGNOR:
BRAMS, PETER

DOC DATE: 11/13/1995

ASSIGNOR:
HANNA, NABIL

DOC DATE: 11/13/1995

ASSIGNOR:
SHESTOWSKY, WILLIAM S.

DOC DATE: 11/14/1995

ASSIGNEE:
IDEC PHARMACEUTICALS CORPORATION
11011 TORREYANA ROAD
SAN DIEGO, CALIFORNIA 92121

SERIAL NUMBER: 08487550
PATENT NUMBER:

FILING DATE: 06/07/1995
ISSUE DATE:

DOCKETED
Idec 012712-131

JACQUELINE MOORE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

012712-131
Attorney's Docket No.

ASSIGNMENT
(JOINT)

THIS ASSIGNMENT, by DARRELL R. ANDERSON, PETER BRAMS, NABIL HANNA and BILL SHESTOWSKY (hereinafter referred to as "the Assignors"), residing at 1851 NAVAJO PLACE, ESCONDIDO, CA 92029; 4260 3RD AVENUE, #101, SAN DIEGO, CA 92103; 3255 FORTUNA RANCH ROAD, OLIVENHAIN, CA 92024; 1155 THOMAS AVENUE, SAN DIEGO, CA 92109; 4311 ROBBINS STREET, SAN DIEGO, CA 92122; and 1225 VIA MONTORO, ENCINITAS, CA 92024, respectively, witnesseth:

WHEREAS, the Assignors have invented certain new and useful improvements in MONKEY MONOCLONAL ANTIBODIES SPECIFIC TO HUMAN B7.1 AND/OR B7.2 PRIMATIZED FORMS THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING, AND USE THEREOF AS IMMUNOSUPPRESSANTS set forth in an application for Letters Patent of the United States, [ ] having an oath or declaration executed on even date herewith; [X] bearing Application No. 08/487,550, and filed on JUNE 7, 1995; and

WHEREAS, IDEC PHARMACEUTICALS CORPORATION, a corporation duly organized under and pursuant to the laws of CALIFORNIA and having its principal place of business at 11011 TORREYANA ROAD, SAN DIEGO, CA 92121 (hereinafter referred to as "the Assignee"), is desirous of acquiring the entire right, title, and interest in and to said inventions and said application for Letters Patent of the United States, and in and to any Letters Patent or Patents, United States or foreign, to be obtained therefor and thereon.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and sufficient consideration, the receipt of which is hereby acknowledged, the Assignors have sold, assigned, transferred, and set over, and by these presents do sell, assign, transfer, and set over, unto the Assignee, its successors, legal representatives, and assigns the entire right, title, and interest in and to the above-mentioned inventions, application for Letters Patent, and any and all Letters Patent or Patents of the United States of America and all foreign countries that may be granted therefor and thereon, and in and to any and all divisions, continuations, and continuations-in-part of said application, and reissues and extensions of said Letters Patent or Patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors, legal representatives, and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted as fully and entirely as the same would have been held and enjoyed by the Assignors had this sale and assignment not been made;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns, that, at the time of execution and delivery of these presents, the Assignors are the sole and lawful owners of the entire right, title, and interest in and to the inventions and application for Letters Patent above-mentioned, and that the same are unencumbered, and that the Assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns that the Assignors will, whenever counsel of the Assignee, or the counsel of its successors, legal representatives, and assigns, shall advise that any proceeding in connection with said inventions or said application for Letters Patent, or any proceeding in connection with Letters Patent for said inventions in any country, including

interference proceedings, is lawful and desirable, or that any division, continuation, or continuation-in-part of any application for Letters Patent, or any reissue or extension of any Letters Patent to be obtained thereon, is lawful and desirable, sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done for the procurement, maintenance, enforcement, and defense of Letters Patent for said inventions, without charge to the Assignee, its successors, legal representatives, and assigns, but at the cost and expense of the Assignee, its successors, legal representatives, and assigns;

AND the Assignors hereby request the Commissioner of Patents to issue said Letters Patent of the United States to the Assignee as the Assignee of said inventions, the Letters Patent to be issued for the sole use and behalf of the Assignee, its successors, legal representatives, and assigns.

Date 11/13/95 Name of Assignor D. R. Anderson
Darrell R. ANDERSON

Date 11-13-95 Name of Assignor Peter Brams
Peter BRAMS

Date 11/13/95 Name of Assignor Nabil Hanna
Nabil HANNA

Date 11/14/95 Name of Assignor William S. Shestowsky
Bill SHESTOWSKY

05-23-1996

581-40

FORM PTO-1595
(Rev. 6/93)

100181709

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SHEET

Attorney's Docket No. 012712-131

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

MRD 5-23-96

(1)Darrell R. Anderson
(2)Peter Brams
(3)Nabil Hanna
(4)William S. Shestowsky

Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

2. Name and address of receiving party(ies):

Name: IDEC Pharmaceuticals Corporation

Address: 11011 Torreyana Road

San Diego, CA 92121

Additional name(s) & address(es) attached? [ ] Yes [X] No

3. Nature of conveyance:

[X] Assignment
[ ] Security Agreement
[ ] Merger
[ ] Change of Name

Other:

Execution Date: (1) 11/13/95 (2) 11/13/95 (3) 11/13/95 (4) 11/14/95

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)

08/487,550

B. Patent No.(s)

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Robin L. Teskin, Esq.

Address: Burns, Doane, Swecker & Mathis, LLP

Post Office Box 1404

Alexandria, Virginia 22313-1404

6. Total number of applications and patents involved: 1

620 GT 05/28/96 08487550
1 581 40.00 CK 012712-131

7. Total fee (37 CFR 3.41): $40.00

[X] Enclosed

[X] Authorized to be charged to deposit account, if necessary

8. Deposit account number:

02-4800

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

40E Chg 30 Spec Fee

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Robin L. Teskin
Name of Person Signing

Robin L Teskin
Signature

May 23, 1996
Date

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

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(BDSM 8)
(5/95)

APPENDIX C

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APRIL 21, 1997

PTAS

BURNS, DOANE, SWECKER & MATHIS, L.L.P.
ROBIN L. TESKIN
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

100362581A

UNITED STATES PATENT AND TRADEMARK OFFICE
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PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/31/1997

REEL/FRAME: 8359/0655
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ANDERSON, DARRELL R.

DOC DATE: 01/14/1997

ASSIGNOR:
HANNA, NABIL

DOC DATE: 01/14/1997

ASSIGNOR:
BRAMS, PETER

DOC DATE: 01/20/1997

ASSIGNEE:
IDEC PHARMACEUTICALS CORPORATION
11011 TORREYANA ROAD
SAN DIEGO, CALIFORNIA 92121

SERIAL NUMBER: 08746361
PATENT NUMBER:

FILING DATE: 11/08/1996
ISSUE DATE:

BURNS, DOANE, SWECKER & MATHIS, L.L.P.
RECEIVED
APR 23 1997
DOCKETED

P27371A

01712-256
EJG/ALT
IDec

PEARLENE FOSTER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

FORM PTO-1595
(Rev. 6/93)

02-26-1997

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET

Attorney's Docket No. 012712-256

100362581

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Darrell R. Anderson, Nabil Hanna and Peter Brams

Additional name(s) of conveying party(ies) attached? [ ] Yes [X] No

3. Nature of conveyance:

[X] Assignment [ ] Merger
[ ] Security Agreement [ ] Change of Name

Other: _____

Execution Date: January 14, January 14, and January 20, 1997

2. Name and address of receiving party(ies):

Name: IDEC Pharmaceuticals Corporation

Address: 11011 Torreyana Road

San Diego, California 92121

UNITED STATES OF AMERICA

Additional name(s) & address(es) attached? [ ] Yes [X] No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: January 14, January 14 and January 20, 1997

A. Patent Application No.(s)

08/746,361

B. Patent No.(s)

50161 U.S. PTO
02/25/97

Additional numbers attached? [ ] Yes [X] No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Robin L. Teskin

Address: BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Post Office Box 1404

Alexandria, Virginia 22313-1404

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): $40.00

[X] Enclosed

[X] Authorized to be charged to deposit account, if necessary

8. Deposit account number:

02-4800

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Robin L. Teskin, Reg. No. 35,030
Name of Person Signing

Robin L Teskin
Signature

1/31/97
Date

Total number of pages including cover sheet, attachments, and document: 3

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

300 SD 02/12/97 08746361
1 581 40.00 CK

(BDSM 8)
(4/96)

012712-256
Attorney's Docket No.

ASSIGNMENT
(JOINT)

THIS ASSIGNMENT, by DARRELL R. ANDERSON, NABIL HANNA, and PETER BRAMS, residing at 1851 NAVAJO PLACE, ESCONDIDO, CA 92029, 3255 FORTUNA RANCH ROAD, OLIVENHAIN, CA 92024 and 4260 3RD AVENUE, #101, SAN DIEGO, CA 92103 (hereinafter referred to as "the Assignors"), respectively, witnesseth:

WHEREAS, the Assignors have invented certain new and useful improvements in IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 CO-STIMULATORY ANTIGENS set forth in an application for Letters Patent of the United States, [ ] which is a provisional application to be filed herewith; [ ] which is a non-provisional application having an oath or declaration executed on even date herewith prior to filing of application; [X] bearing Application No. 08/746,361, and filed on NOVEMBER 8, 1996; and

WHEREAS, IDEC PHARMACEUTICALS CORPORATION, a corporation duly organized under and pursuant to the laws of THE STATE OF CALIFORNIA and having its principal place of business at 11011 TORREYANA ROAD, SAN DIEGO, CA 92121 (hereinafter referred to as "the Assignee"), is desirous of acquiring the entire right, title, and interest in and to said inventions, the right to file applications on said inventions and the entire right, title and interest in and to any applications, including provisional applications for Letters Patent of the United States or other countries claiming priority to said application, and in and to any Letters Patent or Patents, United States or foreign, to be obtained therefor and thereon.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and sufficient consideration, the receipt of which is hereby acknowledged, the Assignors have sold, assigned, transferred, and set over, and by these presents do sell, assign, transfer, and set over, unto the Assignee, its successors, legal representatives, and assigns the entire right, title, and interest in and to the above-mentioned inventions, the right to file applications on said inventions and the entire right, title and interest in and to any applications for Letters Patent of the United States or other countries claiming priority to said applications, and any and all Letters Patent or Patents of the United States of America and all foreign countries that may be granted therefor and thereon, and in and to any and all applications claiming priority to said applications, divisions, continuations, and continuations-in-part of said applications, and reissues and extensions of said Letters Patent or Patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors, legal representatives, and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted as fully and entirely as the same would have been held and enjoyed by the Assignors had this sale and assignment not been made;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns, that, at the time of execution and delivery of these presents, the Assignors are the sole and lawful owners of the entire right, title, and interest in and to the inventions set forth in said applications and said applications, including provisional applications, above-mentioned, and that the same are unencumbered, and that the Assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns that the Assignors will, whenever

counsel of the Assignee, or the counsel of its successors, legal representatives, and assigns, shall advise that any proceeding in connection with said inventions or said applications for Letters Patent or Patents, or any proceeding in connection with Letters Patent or Patents for said inventions in any country, including interference proceedings, is lawful and desirable, or that any application claiming priority to said application, division, continuation, or continuation-in-part of any applications for Letters Patent or Patents, or any reissue or extension of any Letters Patent or Patents to be obtained thereon, is lawful and desirable, sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done for the procurement, maintenance, enforcement, and defense of Letters Patent or Patents for said inventions, without charge to the Assignee, its successors, legal representatives, and assigns, but at the cost and expense of the Assignee, its successors, legal representatives, and assigns;

AND the Assignors hereby authorize and request the attorneys of BURNS, DOANE, SWECKER & MATHIS, L.L.P. of Alexandria, Virginia, to insert in the spaces provided above the filing date, application number, and attorney docket number of said application when known.

AND the Assignors hereby request the Commissioner of Patents to issue any and all said Letters Patent of the United States to the Assignee as the Assignee of said inventions, the Letters Patent to be issued for the sole use and behalf of the Assignee, its successors, legal representatives, and assigns.

Date 1/14/97 Signature of Assignor _____
Darrell R. ANDERSON

Date 1/14/97 Signature of Assignor _____
Nabil HANNA

Date 01-20-97 Signature of Assignor _____
Peter BRAMS

APPENDIX D

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

SEPTEMBER 03, 2004

PTAS

700106103A

PILLSBURY WINTHROP LLP
THOMAS A. CAWLEY, JR.
P.O. BOX 10500
INTELLECTUAL PROPERTY GROUP
MCLEAN, VA 22102

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RECORDATION DATE: 08/06/2004

REEL/FRAME: 015044/0873
NUMBER OF PAGES: 7

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
IDEC PHARMACEUTICALS CORPORATION

DOC DATE: 11/12/2003

ASSIGNEE:
BIOGEN IDEC INC.
3030 CALLAN ROAD
SAN DIEGO, CALIFORNIA 92121

SERIAL NUMBER: 07431426
PATENT NUMBER:
TITLE: ANTI-IDIOTYPE ANTIBODIES TO HUMAN MELANOMA-ASSOCIATED PROTEOGLYCAN ANTIGEN

FILING DATE: 11/03/1989
ISSUE DATE:

SERIAL NUMBER: 07735064
PATENT NUMBER:
TITLE: CHIMERIC ANTIBODIES FOR HUMAN THERAPY

FILING DATE: 07/25/1991
ISSUE DATE:

SERIAL NUMBER: 07735069 FILING DATE: 07/25/1991
PATENT NUMBER: ISSUE DATE:
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 07856281 FILING DATE: 03/23/1992
PATENT NUMBER: ISSUE DATE:
TITLE: CHIMERIC ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 07912292 FILING DATE: 07/10/1992
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 07977691 FILING DATE: 11/13/1992
PATENT NUMBER: ISSUE DATE:
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE FOR ENHANCEMENT OF EXPRESSION OF CO-LINKED GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 08476674 FILING DATE: 06/07/1995
PATENT NUMBER: ISSUE DATE:
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 08746361 FILING DATE: 11/08/1996
PATENT NUMBER: ISSUE DATE:
TITLE: IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 CO-STIMULATORY ANTIGENS

SERIAL NUMBER: 08933359 FILING DATE: 09/18/1997
PATENT NUMBER: ISSUE DATE:
TITLE: SYNERGISTIC COMPOSITION AND METHODS FOR TREATINGNEOPLASTIC OR CANCEROUS GROWTHS AND FOR RESTORING OR BOOSTING HEMATOPOIESIS

SERIAL NUMBER: 09082472 FILING DATE: 05/21/1998
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 09149479 FILING DATE: 09/08/1998
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PRODUCING HUMAN ANTIBODIES IN SCID MICE WHICH USES DENDRITIC CELLS PULSED WITH ANTIGEN-ANTIBODY COMPLEXES AND ANTIGEN-ANTIBODY COMPLEXES AS IMMUNIZING AGENTS

SERIAL NUMBER: 09615796 FILING DATE: 07/13/2000
PATENT NUMBER: ISSUE DATE:
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 09834933 FILING DATE: 04/16/2001
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B CELL MALIGNANCIES USING ANTI-CD40L ANTIBODIES IN COMBINATION WITH ANTI-CD20 ANTIBODIES AND/OR CHEMOTHERAPEUTICS AND RADIOTHERAPY

SERIAL NUMBER: 09850165 FILING DATE: 05/08/2001
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 09877065 FILING DATE: 06/11/2001
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF OVARIAN CARCINOMAS

SERIAL NUMBER: 09971631 FILING DATE: 10/09/2001
PATENT NUMBER: ISSUE DATE:
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 60057831 FILING DATE: 09/08/1997
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PRODUCING HUMAN ANTIBODIES IN SCID MICE WHICH USES DENDRITIC CELLS PULSED WITH ANTIGEN-ANTIBODY COMPLEXES AND ANTIGEN-ANTIBODY COMPLEXES AS IMMUNIZING AGENTS

SERIAL NUMBER: 60109607 FILING DATE: 11/23/1998
PATENT NUMBER: ISSUE DATE:
TITLE: TUMOR ANTIGEN-SPECIFIC ANTIBODY-GP39 CHIMERIC PROTEIN CONSTRUCTS

SERIAL NUMBER: 60134848 FILING DATE: 05/19/1999
PATENT NUMBER: ISSUE DATE:
TITLE: OVERCOMING BARRIERS TO ADENOVIRUS VECTOR-MEDIATED GENE THERAPY FOR CYSTIC FIBROSIS

SERIAL NUMBER: 60148288 FILING DATE: 08/11/1999
PATENT NUMBER: ISSUE DATE:
TITLE: NEW CLINICAL PARAMETERS FOR DETERMINING HEMATOLOGIC TOXICITY PRIOR TO RADIOIMMUNOTHERAPY

SERIAL NUMBER: 60185390 FILING DATE: 02/28/2000
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PRAPARING ANTI-MIF ANTIBODIES

SERIAL NUMBER: 60189050 FILING DATE: 03/14/2000
PATENT NUMBER: ISSUE DATE:
TITLE: TWO MONOCLONAL ANTIBODIES THAT BIND PHOSPHATIDYL SERINE AND A METHOD OF KILLING TUMOR CELLS

SERIAL NUMBER: 60193467 FILING DATE: 03/31/2000
PATENT NUMBER: ISSUE DATE:
TITLE: COMBINED USE OF ANTI-CYTOKINE ANTIBODIES AND ANTI-CD20 FOR THE TREATMENT OF B-CELL LYMPHOMA

SERIAL NUMBER: 60199365 FILING DATE: 04/25/2000
PATENT NUMBER: ISSUE DATE:
TITLE: INTRATHECAL ADMINISTRATION OF RITUXIMAB FOR TREATMENT OF CENTRAL NERVOUS SYSTEM LYMPHOMAS

SERIAL NUMBER: 60209584 FILING DATE: 06/06/2000
PATENT NUMBER: ISSUE DATE:
TITLE: NON-AGONISTRIC ANTIBODIES TO HUMAN GP39, COMPOSITIONS CONTAINING AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 60210451 FILING DATE: 06/09/2000
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF OVARIAN CARCINOMAS

SERIAL NUMBER: 60212668 FILING DATE: 06/20/2000
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B-CELL ASSOCIATED DISEASES SUCH AS MALIGNANCIES AND AUTOMMUNE DISEASES USING ANTI-CD20 ANTIBODY/RADIOLABLED ANTI-CD22 ANTIBODY COMBINATION

SERIAL NUMBER: 60213252 FILING DATE: 06/22/2000
PATENT NUMBER: ISSUE DATE:
TITLE: BISPECIFIC FUSION PROTEIN AND METHOD OF USE FOR ENHANCING EFFECTOR CELL KILLING OF TARGET CELLS

SERIAL NUMBER: 60217706 FILING DATE: 07/12/2000
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B CELL MALIGNANCIES USING ANTOI-CD40L ANTIBODIES IN COMBINATION WITH ANTI-CD20 ANTIBODIES AND/OR CHEMTHERAPETICS AND RADIOTHERAPY

SERIAL NUMBER: 60233607 FILING DATE: 09/18/2000
PATENT NUMBER: ISSUE DATE:
TITLE: COMBINATION THERAPY FOR TREATMENT OF AUTOIMMUNE DISEASES COMPRISING CD40L ANTAGONIST AND ANTIBODIES TO B7,CD19,CD20,CD22,CD23

SERIAL NUMBER: 60233625 FILING DATE: 09/18/2000
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PREPARING ANTI-MIF ANTIBODIES

SERIAL NUMBER: 60241022 FILING DATE: 10/20/2000
PATENT NUMBER: ISSUE DATE:
TITLE: VARIANT LGG3 RITUXAN AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 60257147 FILING DATE: 12/22/2000
PATENT NUMBER: ISSUE DATE:
TITLE: COMBINATION THERAPY FOR TREATMENT OF AUTOIMMUNE DISEASES USING B CELL DEPLETING/IMMUNOREGULATORY ANTIBODY COMBINATION

SERIAL NUMBER: 60264318 FILING DATE: 01/29/2001
PATENT NUMBER: ISSUE DATE:
TITLE: MODIFIED ANTIBODIES AND METHODS OF USE

SERIAL NUMBER: 60280139 FILING DATE: 04/02/2001
PATENT NUMBER: ISSUE DATE:
TITLE: EXPRESSION OF GNTIII IN A RECOMBINANT ANTI-CD20 CHO PRODUCTION CELL LINE: EXPRESSION OF ANTIBODIES WITH ALTERED GLYCOFORMS LEADS TO AN INCREASE IN ADCC THROUGH HIGHER AFFINITY FOR FCYRIII

SERIAL NUMBER: 60300063 FILING DATE: 06/25/2001
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60303813 FILING DATE: 07/10/2001
PATENT NUMBER: ISSUE DATE:
TITLE: INHIBITION OF APOPTOSIS PROCESS AND IMPROVEMENT OF CELL PERFORMANCE

SERIAL NUMBER: 60331187 FILING DATE: 11/09/2001
PATENT NUMBER: ISSUE DATE:
TITLE: ANTI CD 80 AND RITUXIMAB COMBINATION THERAPY OF B-CELL LYMPHOMA

SERIAL NUMBER: 60331481 FILING DATE: 11/16/2001
PATENT NUMBER: ISSUE DATE:
TITLE: POLYCISTRONIC EXPRESSION OF ANTIBODIES

SERIAL NUMBER: 60341860 FILING DATE: 12/21/2001
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60357140 FILING DATE: 02/19/2002
PATENT NUMBER: ISSUE DATE:
TITLE: PROSTATE SPECIFIC GENES AND THE USE THEREOF IN DESIGN OR THERAPEUTICS

SERIAL NUMBER: 60367727 FILING DATE: 03/28/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF COLON CARCINOMAS

SERIAL NUMBER: 60381328 FILING DATE: 05/20/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF COLON CARCINOMAS

SERIAL NUMBER: 60386746 FILING DATE: 06/10/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES UPREGULATED IN BREAST CANCER AND USE THEREOF AS TARGETS FOR NOVEL THERAPIES AND DIAGNOSTIC AGENTS

SERIAL NUMBER: 60386747 FILING DATE: 06/10/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF COLON CARCINOMAS

SERIAL NUMBER: 60386748 FILING DATE: 06/10/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60386759 FILING DATE: 06/10/2002
PATENT NUMBER: ISSUE DATE:
TITLE: PROSTATE SPECIFIC GENES AND THE USE THEREOF IN DESIGN OF THERAPEUTICS

SERIAL NUMBER: 60390191 FILING DATE: 06/21/2002
PATENT NUMBER: ISSUE DATE:
TITLE: BUFFERED FORMULATIONS FOR CONCENTRATING ANTIBODIES

SERIAL NUMBER: 60396082 FILING DATE: 07/17/2002
PATENT NUMBER: ISSUE DATE:
TITLE: PROSTATE SPECIFIC GENES AND THE USE THEREOF IN DESIGN OF THERAPEUTICS

SERIAL NUMBER: 60396141 FILING DATE: 07/17/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60396255 FILING DATE: 07/17/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES UPREGULATED IN BREAST CANCER

SERIAL NUMBER: 60400687 FILING DATE: 08/05/2002
PATENT NUMBER: ISSUE DATE:
TITLE: POLYCISTRONIC EXPRESSION OF ANTIBODIES

SERIAL NUMBER: 60405318 FILING DATE: 08/23/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES UPREGULATED IN BREAST CANCER

SERIAL NUMBER: 60405319 FILING DATE: 08/23/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60410506 FILING DATE: 09/13/2002
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD OF PURIFYING ANTIBODIES BY SIMULATED MOVING BED CHROMATOGRAPHY

SERIAL NUMBER: 60427564 FILING DATE: 11/20/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL GENE TARGETS AND LIGANDS THAT BIND THERETO FOR TREATMENT AND DIAGNOSIS OF COLON CARCINOMAS

SERIAL NUMBER: 60428274 FILING DATE: 11/22/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES CORRELATED TO OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS

SERIAL NUMBER: 60452928 FILING DATE: 03/10/2003
PATENT NUMBER: ISSUE DATE:
TITLE: THIOL-MEDIATED DRUG ATTACHMENT TO TARGETING PEPTIDES

SERIAL NUMBER: 09238741 FILING DATE: 01/28/1999
PATENT NUMBER: ISSUE DATE:
TITLE: PRODUCTION OF TETRAVALENT ANTIBODIES

SERIAL NUMBER: 09259337 FILING DATE: 03/01/1999
PATENT NUMBER: ISSUE DATE:
TITLE: RADIOLABELING KIT AND BINDING ASSAY

SERIAL NUMBER: 09259338 FILING DATE: 03/01/1999
PATENT NUMBER: ISSUE DATE:
TITLE: KIT FOR RADIOLABELING LIGANDS WITH YTTRIUM-90

SERIAL NUMBER: 09435992 FILING DATE: 11/08/1999
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B CELL MALIGNANCIES USING ANTI-CD40L ANTIBODIES IN COMBINATION WITH ANTI-CD20 ANTIBODIES AND/OR CHEMOTHERAPEUTICS AND RADIOTHERAPY

SERIAL NUMBER: 09447594 FILING DATE: 11/23/1999
PATENT NUMBER: ISSUE DATE:
TITLE: TUMOR ANTIGEN-SPECIFIC ANTIBODY-GP39 CHIMERIC PROTEIN CONSTRUCTS

SERIAL NUMBER: 09576424 FILING DATE: 05/22/2000
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF CROHN'SDISEASE USING ANTI-CD80 ANTIBODIES THAT DO NOT INHIBIT THE BINDING OF CD80 ANTIGENTO CTLA-4

SERIAL NUMBER: 09612914 FILING DATE: 07/10/2000
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTI-CD4 ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 09628186 FILING DATE: 07/28/2000
PATENT NUMBER: ISSUE DATE:
TITLE: KIT FOR RADIOLABELING LIGANDS WITH YTTRIUM-90

SERIAL NUMBER: 09635929 FILING DATE: 08/10/2000
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMEANT OF PATIENTS HAVING NON-HODGKINS LYMPHOMA WITH BONE MARROW INVOLVEMENT WITH ANTI-CD20 ANTIBODIES

SERIAL NUMBER: 09758173 FILING DATE: 01/12/2001
PATENT NUMBER: ISSUE DATE:
TITLE: METHODS FOR TREATING B CELL LYMPHONA USING CD80-SPECIFIC ANTIBODIES

SERIAL NUMBER: 09772938 FILING DATE: 01/31/2001
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF CELL MALIGNANCIES USING COMBINATION OF B CELL DEPLETING ANTIBODY AND IMMUNE MODULATING ANTIBODY RELATED APPLICATIONS

SERIAL NUMBER: 09791551 FILING DATE: 02/26/2001
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PREPARING ANTI-MIF ANTIBODIES

SERIAL NUMBER: 09798525 FILING DATE: 02/21/2001
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD FOR PRODUCING HUMAN ANTIBODIES IN SCID MICE WHICH USES DENDRITIC CELLS PULSED WITH ANTIGEN-ANTIBODY COMPLEXES AND ANTIGEN-ANTIBODY COMPLEXES AS IMMUNIZING AGENTS

SERIAL NUMBER: 09805217 FILING DATE: 03/14/2001
PATENT NUMBER: ISSUE DATE:
TITLE: ANTIBODIES THAT BIND PHOSPHATIDYL SERINE AND A METHOD OF THEIR USE

SERIAL NUMBER: 09822672 FILING DATE: 04/02/2001
PATENT NUMBER: ISSUE DATE:
TITLE: COMBINED USE OF ANTI-CYTOKINE ANTIBODIES OR ANTAGONISTS AND ANTI-CD20 FOR TREATMENT OF B CELL LYMPHOMA

SERIAL NUMBER: 09840872 FILING DATE: 04/25/2001
PATENT NUMBER: ISSUE DATE:
TITLE: INTRATHECAL ADMINISTRATION OF RITUXIMAB FOR TREATMENT OF CENTRAL NERVOUS SYSTEM LYMPHOMAS

SERIAL NUMBER: 09853580 FILING DATE: 05/14/2001
PATENT NUMBER: ISSUE DATE:
TITLE: SYNERGISTIC COMPOSITION AND METHODS FOR TREATING NEOPLASTIC OR CANCEROUS GROWTHS AND FOR RESTORING OR BOOSTING HEMATOPOIESIS

SERIAL NUMBER: 09853581 FILING DATE: 05/14/2001
PATENT NUMBER: ISSUE DATE:
TITLE: SYNERGISTIC COMPOSITION AND METHODS FOR TREATING NEOPLASTIC OR CANCEROUS GROWTHS AND FOR RESTORING OR BOOSTING HEMATOPOIESIS

SERIAL NUMBER: 09855717 FILING DATE: 05/16/2001
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B CELL MALIGNANCIES USING COMBINATION OF B CELL DEPLETING ANTIBODY AND IMMUNE MODULATING ANTIBODY RELATED APPLICATIONS

SERIAL NUMBER: 09856534 FILING DATE: 09/04/2001
PATENT NUMBER: ISSUE DATE:
TITLE: TUMOR ANTIGEN- SPECIFIC ANTIBODY- GP39 CHIMERIC PROTEIN CONSTRUCTS

SERIAL NUMBER: 09874141 FILING DATE: 06/06/2001
PATENT NUMBER: ISSUE DATE:
TITLE: NON-AGONISTIC ANTIBODIES TO HUMAN GP39, COMPOSITIONS CONTAINING, AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 09883962 FILING DATE: 06/20/2001
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B-CELL ASSOCIATED DISEASES SUCH AS MALIGNANCES AND AUTOIMMUNE DISEASES USING A COLD ANTI-CD20 ANTIBODY/RADIOLABELED ANTI-CD22 ANTIBODY COMBINATION

SERIAL NUMBER: 09954274 FILING DATE: 09/18/2001
PATENT NUMBER: ISSUE DATE:
TITLE: COMBINATION THERAPY FOR TREATMENT OF AUTOIMMUNE DISEASES USING B CELL DEPLETING/IMMUNOREGULATORY ANTIBODY COMBINATION

SERIAL NUMBER: 09982849 FILING DATE: 10/22/2001
PATENT NUMBER: ISSUE DATE:
TITLE: VARIANT IGG3 RITUXAN AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 09985646 FILING DATE: 11/05/2001
PATENT NUMBER: ISSUE DATE:
TITLE: USE OF CD23 ANTAGONISTS FOR THE TREATMENT OF NEOPLASTIC DISORDERS

SERIAL NUMBER: 09986174 FILING DATE: 11/07/2001
PATENT NUMBER: ISSUE DATE:
TITLE: BISPECIFIC FUSION PROTEIN AND METHOD OF USE FOR ENHANCING EFFECTOR CELL KILLING OF TARGET CELLS

SERIAL NUMBER: 10058120 FILING DATE: 01/29/2002
PATENT NUMBER: ISSUE DATE:
TITLE: MODIFIED ANTIBODIES AND METHODS OF USE

SERIAL NUMBER: 10073138 FILING DATE: 02/13/2002
PATENT NUMBER: ISSUE DATE:
TITLE: IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 CO-STIMULATORY ANTIGENS

SERIAL NUMBER: 10096963 FILING DATE: 03/14/2002
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B CELL MALIGNANCIES USING ANTI-CD40L ANTIBODIES IN COMBINATION WITH ANTI-CD20 ANTIBODIES AND/OR CHEMOTHERAPEUTICS AND RADIOTHERAPY

SERIAL NUMBER: 10109853 FILING DATE: 04/01/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NOVEL METHOD FOR INTEGRATING GENES AT SPECIFIC SITES IN MAMMALIAN CELLS VIA HOMOLOGOUS RECOMBINATION AND VECTORS FOR ACCOMPLISHING THE SAME

SERIAL NUMBER: 10113929 FILING DATE: 04/02/2002
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTIBODIES COEXPRESSED WITH GNTIII

SERIAL NUMBER: 10171680 FILING DATE: 06/17/2002
PATENT NUMBER: ISSUE DATE:
TITLE: HUMANIZED ANTIBODIES TO HUMAN GP39, COMPOSITIONS CONTAINING AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 10171681 FILING DATE: 06/17/2002
PATENT NUMBER: ISSUE DATE:
TITLE: TREATING AUTOIMMUNE DISEASES WITH HUMANIZED ANTI-CD40L ANTIBODY

SERIAL NUMBER: 10191052 FILING DATE: 07/10/2002
PATENT NUMBER: ISSUE DATE:
TITLE: INHIBITION OF APOPTOSIS PROCESS AND IMPROVEMENT OF CELL PERFORMANCE

SERIAL NUMBER: 10195426 FILING DATE: 07/16/2002
PATENT NUMBER: ISSUE DATE:
TITLE: NEW CLINICAL PARAMETERS FOR DETERIMING HEMATOLOGIC TOXICITY PRIOR TO RADIOIMMUNOTHERAPY

SERIAL NUMBER: 10211357 FILING DATE: 08/05/2002
PATENT NUMBER: ISSUE DATE:
TITLE: RECOMBINANT ANTI-CD4 ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 10241832 FILING DATE: 09/12/2002
PATENT NUMBER: ISSUE DATE:
TITLE: USE OF CD23 ANTAGONISTS FOR THE TREATMENT OF NEOPLASTIC DISORDERS

SERIAL NUMBER: 10241836 FILING DATE: 09/12/2002
PATENT NUMBER: ISSUE DATE:
TITLE: IMMUNOREGULATORY ANTIBODIES AND USES THEREOF

SERIAL NUMBER: 10291532 FILING DATE: 11/12/2002
PATENT NUMBER: ISSUE DATE:
TITLE: ANTI-CD80 ANTIBODY HAVING ADCC ACTIVITY FOR ADCC MEDIATED KILLING OF B CELL LYMPHOMA CELLS ALONE OR IN COMBINATION WITH OTHER THERAPIES

SERIAL NUMBER: 10295823 FILING DATE: 11/18/2002
PATENT NUMBER: ISSUE DATE:
TITLE: POLYCISTRONIC EXPRESSION OF ANTIBODIES

SERIAL NUMBER: 10326924 FILING DATE: 12/23/2002
PATENT NUMBER: ISSUE DATE:
TITLE: GENES OVEREXPRESSED BY OVARIAN CANCER AND THEIR USE IN DEVELOPING NOVEL THERAPEUTICS, ESPECIALLY ANTIBODIES

SERIAL NUMBER: 10367978 FILING DATE: 02/19/2003
PATENT NUMBER: ISSUE DATE:
TITLE: PROSTATE SPECIFIC GENES AND THE USE THEREOF IN DESIGN OR THERAPEUTICS

SERIAL NUMBER: 10384356 FILING DATE: 03/10/2003
PATENT NUMBER: ISSUE DATE:
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 10661086 FILING DATE: 09/12/2003
PATENT NUMBER: ISSUE DATE:
TITLE: METHOD OF PURIFYING POLYPEPTIDES BY SIMULATED MOVING BED CHROMATOGRAPHY

SERIAL NUMBER: 10743398 FILING DATE: 12/23/2003
PATENT NUMBER: ISSUE DATE:
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 10743739 FILING DATE: 12/24/2003
PATENT NUMBER: ISSUE DATE:
TITLE: SYNERGISTIC COMPOSITION AND METHODS FOR TREATING NEOPLASTIC OR CANCEROUS GROWTHS AND FOR RESTORING OR BOOSTING HEMATOPOIESIS

SERIAL NUMBER: 60148287 FILING DATE: 08/11/1999
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF PATIENTS HAVING NON-HODGKINS LYMPHOMA WITH BONE MARROW INVOLVEMENT WITH ANTI-CD20 ANTIBODIES

SERIAL NUMBER: 60479910 FILING DATE: 06/20/2003
PATENT NUMBER: ISSUE DATE:
TITLE: USE OF DEPTH FILTRATION AND CONTINUOUS CENTRIFUGATION TO CLARIFY CELL SAMPLES

SERIAL NUMBER: 60510552 FILING DATE: 10/14/2003
PATENT NUMBER: ISSUE DATE:
TITLE: LECTIN AFFINITY PURIFICATION AND IDENTIFICATION OF PROTEINS OF VASCULAR TISSUE ASSOCIATED WITH A DISEASE OR DISORDER

SERIAL NUMBER: 10703669 FILING DATE: 11/10/2003
PATENT NUMBER: ISSUE DATE:
TITLE: TREATMENT OF B-CELL ASSOCIATED DISEASES SUCH AS MALIGNANCIES AND AUTOIMMUNE DISEASES USING A COLD ANTI-CD20 ANTIBODY/RADIOLABELED ANTI-CD22 ANTIBODY COMBINATION

SERIAL NUMBER: 10796158 FILING DATE: 03/10/2004
PATENT NUMBER: ISSUE DATE:
TITLE: THIOL-MEDIATED DRUG ATTACHMENT TO TARGETING PEPTIDES

SERIAL NUMBER: 10871261 FILING DATE: 06/21/2004
PATENT NUMBER: ISSUE DATE:
TITLE: USE OF DEPTH FILTRATION IN SERIES WITH CONTINUOUS CENTRIFUGATION TO CLARIFY MAMMALIAN CELL CULTURES

SERIAL NUMBER: 10058069 FILING DATE: 01/29/2002
PATENT NUMBER: ISSUE DATE:
TITLE: ENGINEERED TETRAVALENT ANTIBODIES AND METHODS OF USE

SERIAL NUMBER: 07680808 FILING DATE: 03/12/1991
PATENT NUMBER: 5270202 ISSUE DATE: 12/14/1993
TITLE: ANTI-IDIOTYPE ANTIBODIES TO HUMAN MELANOMA-ASSOCIATED PROTEOGLYCAN ANTIGEN

SERIAL NUMBER: 07919787 FILING DATE: 07/24/1992
PATENT NUMBER: 5585103 ISSUE DATE: 12/17/1996
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 08147696 FILING DATE: 11/03/1993
PATENT NUMBER: 5648267 ISSUE DATE: 07/15/1997
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 08379072 FILING DATE: 01/25/1995
PATENT NUMBER: 5658570 ISSUE DATE: 08/19/1997
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 08478039 FILING DATE: 06/07/1995
PATENT NUMBER: 5681722 ISSUE DATE: 10/28/1997
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 08481869 FILING DATE: 06/07/1995
PATENT NUMBER: 5693780 ISSUE DATE: 12/02/1997
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 08472311 FILING DATE: 06/07/1995
PATENT NUMBER: 5695770 ISSUE DATE: 12/09/1997
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 08351001 FILING DATE: 12/07/1994
PATENT NUMBER: 5709860 ISSUE DATE: 01/20/1998
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 08484334 FILING DATE: 06/07/1995
PATENT NUMBER: 5733779 ISSUE DATE: 03/31/1998
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 08476349 FILING DATE: 06/07/1995
PATENT NUMBER: 5750105 ISSUE DATE: 05/12/1998
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 08476237 FILING DATE: 06/07/1995
PATENT NUMBER: 5756096 ISSUE DATE: 05/26/1998
TITLE: RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 08488376 FILING DATE: 06/07/1995
PATENT NUMBER: 5811524 ISSUE DATE: 09/22/1998
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 08819866 FILING DATE: 03/14/1997
PATENT NUMBER: 5830698 ISSUE DATE: 11/03/1998
TITLE: NOVEL METHOD FOR INTEGRATING GENES AT SPECIFIC SITES IN MAMMALIAN CELLS VIA HOMOLOGOUS RECOMBINATION AND VECTORS FOR ACCOMPLISHING THE SAME

SERIAL NUMBER: 08634223 FILING DATE: 04/18/1996
PATENT NUMBER: 5840298 ISSUE DATE: 11/24/1998
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 08634224 FILING DATE: 04/18/1996
PATENT NUMBER: 5866125 ISSUE DATE: 02/02/1999
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 08634400 FILING DATE: 04/18/1996
PATENT NUMBER: 5939068 ISSUE DATE: 08/17/1999
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 08635878 FILING DATE: 04/18/1996
PATENT NUMBER: 5955364 ISSUE DATE: 09/21/1999
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 09023715 FILING DATE: 02/13/1998
PATENT NUMBER: 5998144 ISSUE DATE: 12/07/1999
TITLE: METHOD FOR INTEGRATING GENES AT SPECIFIC SITES IN MAMMALIAN CELLS VIA HOMOLOGOUS RECOMBINATION AND VECTORS FOR ACCOMPLISHING THE SAME

SERIAL NUMBER: 08554840 FILING DATE: 11/07/1995
PATENT NUMBER: 6001358 ISSUE DATE: 12/14/1999
TITLE: HUMANIZED ANTIBODIES TO HUMAN GP39, COMPOSITIONS CONTAINING AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 09013092 FILING DATE: 01/26/1998
PATENT NUMBER: 6017733 ISSUE DATE: 01/25/2000
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPRESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 08487550 FILING DATE: 06/07/1995
PATENT NUMBER: 6113898 ISSUE DATE: 09/05/2000
TITLE: HUMAN B7.1-SPECIFIC PRIMATIZED ANTIBODIES AND TRANSFECTOMAS EXPRESSING SAID ANTIBODIES

SERIAL NUMBER: 08523894 FILING DATE: 09/06/1995
PATENT NUMBER: 6136310 ISSUE DATE: 10/24/2000
TITLE: RECOMBINANT ANTI-CD4 ANTIBODIES FOR HUMAN THERAPY

SERIAL NUMBER: 09280999 FILING DATE: 03/30/1999
PATENT NUMBER: 6159730 ISSUE DATE: 12/12/2000
TITLE: IMPAIRED DOMINANT SELECTABLE MARKER SEQUENCE AND INTRONIC INSERTION STRATEGIES FOR ENHANCEMENT OF EXPRESSION OF GENE PRODUCT AND EXPESSION VECTOR SYSTEMS COMPRISING SAME

SERIAL NUMBER: 09024220 FILING DATE: 02/17/1998
PATENT NUMBER: 6197311 ISSUE DATE: 03/06/2001
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 09261207 FILING DATE: 03/03/1999
PATENT NUMBER: 6207858 ISSUE DATE: 03/27/2001
TITLE: REGIOSELECTIVE SYNTHESIS OF DTPA DERIVATIVES

SERIAL NUMBER: 08449728 FILING DATE: 05/24/1995
PATENT NUMBER: 6270769 ISSUE DATE: 08/07/2001
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

SERIAL NUMBER: 09259347 FILING DATE: 03/01/1999
PATENT NUMBER: 6300143 ISSUE DATE: 10/09/2001
TITLE: ELECTROCHEMILUMINESCENT ASSAYS FOR EUKARYOTIC CELLS

SERIAL NUMBER: 09335697 FILING DATE: 06/18/1999
PATENT NUMBER: 6413771 ISSUE DATE: 07/02/2002
TITLE: NEUTRALIZING HIGH AFFINITY HUMAN MONOCLONAL ANTIBODIES SPECIFIC TO RSV F-PROTEIN AND METHODS FOR THEIR MANUFACTURE AND THERAPUTIC USE THEREOF

SERIAL NUMBER: 09343485 FILING DATE: 06/30/1999
PATENT NUMBER: 6413777 ISSUE DATE: 07/02/2002
TITLE: NOVEL METHOD FOR INTEGRATING GENES AT SPECIFIC SITES IN MAMMALIAN CELLS VIA HOMOLOGOUS RECOMBINATION AND VECTORS FOR ACCOMPLISHING THE SAME

SERIAL NUMBER: 08925339 FILING DATE: 09/08/1997
PATENT NUMBER: 6440418 ISSUE DATE: 08/27/2002
TITLE: METHODS OF TREATING AUTOIMMUNE DISEASES WITH GP39-SPECIFIC ANTIBODIES

SERIAL NUMBER: 09625856 FILING DATE: 07/26/2000
PATENT NUMBER: 6451284 ISSUE DATE: 09/17/2002
TITLE: NEW CLINICAL PARAMETERS FOR DETERMINING HEMATOLOGIC TOXICITY PRIOR TO RADIOIMMUNOTHERAPHY

SERIAL NUMBER: 09332595 FILING DATE: 06/14/1999
PATENT NUMBER: 6506383 ISSUE DATE: 01/14/2003
TITLE: HUMANIZED ANTIBODIES OF HUMAN GP39, COMPOSITIONS CONTAINING AND THERAPEUTIC USE THEREOF

SERIAL NUMBER: 09383916 FILING DATE: 08/26/1999
PATENT NUMBER: 6709654 ISSUE DATE: 03/23/2004
TITLE: TREATMENT OF PSORIASIS USING ANTI-B7.1(CD80) ANTIBODIES

SERIAL NUMBER: 09740003 FILING DATE: 12/20/2000
PATENT NUMBER: 6733763 ISSUE DATE: 05/11/2004
TITLE: INDUCTION OF CYTOTOXIC T-LYMPHOCYTE RESPONSES

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RECORDATION FORM COVER SHEET
PATENT APPLICATIONS & PATENTS ONLY

TO THE DIRECTOR OF THE US PATENT AND TRADEMARK OFFICE:
SIR: PLEASE RECORD THE ATTACHED ORIGINAL DOCUMENTS OR COPY THEREOF.

1. NAME OF CONVEYING PARTY(IES) (ASSIGNORS(S)):
1. Idec Pharmaceuticals Corporation
2.
3.
4.
5.
6.
7.
8.

ADDITIONAL NAME(S) OF CONVEYING PARTY(IES) ATTACHED? ☐YES ☒NO

2. PARTY(IES) (ASSIGNEE(S)) RECEIVING INTEREST:

NAME: Biogen Idec Inc.

ADDRESS: 3030 Callan Road, San Diego, California 92121

ADDITIONAL NAME(S) & ADDRESS(ES) ATTACHED? ☐YES ☒NO

3. NATURE OF CONVEYANCE (DOCUMENT):
(Submit herewith only one document for recordation—multiple copies of same Assignment signed by different inventors is one document)

☐ASSIGNMENT OF ☐WHOLE ☐PART INTEREST
☐ORIGINAL ☐FACSIMILE/PHOTOCOPY
☒CHANGE OF NAME ☐VERIFIED TRANSLATION
☐SECURITY ☐MERGER ☐OTHER:

EXEC. DATE: 11/12/03

EXECUTION DATE(S) ON THE DECLARATION IF FILED HEREWITH: (NOTE: IF DATES ON DECLARATION AND ASSIGNMENT DIFFER SEE ATTY!)

4.5 APPL. NO.(S) OR PAT NO.(S). OTHERS ON ADDITIONAL SHEET(S) attached? ☒YES ☐NO

A. PAT. APP. NO.(S) series code/serial no	M#	1st INVENTOR if not in item 1	B. PATENT NO(S)	M#	1st INVENTOR if not in item 1
See Attached Appendix (4 pages)			See Attached Appendix		

5. Name & Address of Party to Whom Correspondence Concerning Document Should be Mailed:

Pillsbury Winthrop LLP
Intellectual Property Group
P.O. Box 10500 McLean, VA 22102

6. NUMBER INVOLVED:
APPLNS 112 + PATS 34 = TOTAL = 146

7. AMOUNT OF FEE DUE: (Code 8021)
ABOVE TOTAL x $40 = $5840

5.5 ATTY DKT:

P 037003-0000051

MATTER NO.	CLIENT REF.

8. PLEASE CHARGE TO OUR DEPOSIT ACCOUNT NUMBER: 03-3975

UNDER ORDER NO	037003	0000051
dup. sheet not required	CLIENT NO.	MATTER NO.

9. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Signature

10. Total number of pages including this cover sheet, attachments and document (do not file dup. Cover sheet): 7

Attorney: Thomas A. Cawley, Jr., Ph.D.
Reg. No. 40944
Atty/Sec: TAC/JBM:sl TEL: (703) 905-2144
Date: August 6, 2004
FAX: (703) 905-2500

FILE WITH PTO RETURN RECEIPT (PAT-103A)

APPENDIX

Patents

Matter No.	Serial No.	Filing Date	Patent No.	Issue Date
281199	07/680,808	March 12, 1991	5,270,202	December 14, 1993
275979	07/919,787	July 24, 1992	5,585,103	December 17, 1996
275402	08/147,696	November 3, 1993	5,648,267	July 15, 1997
275715	08/379,072	January 25, 1995	5,658,570	August 19, 1997
275655	08/478,039	June 7, 1995	5,681,722	October 28, 1997
275656	08/481,869	June 7, 1995	5,693,780	December 2, 1997
275658	08/472,311	June 7, 1995	5,695,770	December 9, 1997
275799	08/351,001	December 7, 1994	5,709,860	January 20, 1998
275403	08/484,334	June 7, 1995	5,733,779	March 31, 1998
275657	08/476,349	June 7, 1995	5,750,105	May 12, 1998
275973	08/476,237	June 7, 1995	5,756,096	May 26, 1998
275757	08/488,376	June 7, 1995	5,811,524	September 22, 1998
275843	08/819,866	March 14, 1997	5,830,698	November 3, 1998
275676	08/634,223	April 18, 1996	5,840,298	November 24, 1998
275679	08/634,224	April 18, 1996	5,866,125	February 2, 1999
275677	08/634,400	April 18, 1996	5,939,068	August 17, 1999
275678	08/635,878	April 18, 1996	5,955,364	September 21, 1999
275844	09/023,715	February 13, 1998	5,998,144	December 7, 1999
275832	08/554,840	November 7, 1995	6,001,358	December 14, 1999
275404	09/013,092	January 26, 1998	6,017,733	January 25, 2000
275942	08/487,550	June 7, 1995	6,113,898	September 5, 2000
275680	08/523,894	September 6, 1995	6,136,310	October 24, 2000
275732	09/280,999	March 30, 1999	6,159,730	December 12, 2000
275801	09/024,220	February 17, 1998	6,197,311	March 6, 2001
275407	09/261,207	March 3, 1999	6,207,858	March 27, 2001
276461	08/449,728	May 24, 1995	6,270,769	August 7, 2001
275831	09/259,347	March 1, 1999	6,300,143	October 9, 2001
275759	09/335,697	June 18, 1999	6,413,771	July 2, 2002
275807	09/343,485	June 30, 1999	6,413,777	July 2, 2002
275833	08/925,339	September 8, 1997	6,440,418	August 27, 2002
275983	09/625,856	July 26, 2000	6,451,284	September 17, 2002
275683	09/332,595	June 14, 1999	6,506,383	January 14, 2003
275716	09/383,916	August 26, 1999	6,709,654	March 23, 2004
275802	09/740,003	December 20, 2000	6,733,763	May 11, 2004

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Applications

Matter No.	Serial No.	Filing Date	Status
281198	07/431,426	November 3, 1989	ABANDONED
275969	07/735,064	July 25, 1991	ABANDONED
275978	07/735,069	July 25, 1991	ABANDONED
275970	07/856,281	March 23, 1992	ABANDONED
275971	07/912,292	July 10, 1992	ABANDONED
275730	07/977,691	November 13, 1992	ABANDONED
275800	08/476,674	June 7, 1995	ABANDONED
275943	08/746,361	November 8, 1996	ABANDONED
275999	08/933,359	September 18, 1997	ABANDONED
275974	09/082,472	May 21, 1998	ABANDONED
277092	09/149,479	September 8, 1998	ABANDONED
275733	09/615,796	July 13, 2000	ABANDONED
280601	09/834,933	April 16, 2001	ABANDONED
280614	09/850,165	May 8, 2001	ABANDONED
280631	09/877,065	June 11, 2001	ABANDONED
282604	09/971,631	October 9, 2001	ABANDONED
277093	60/057,831	September 8, 1997	LAPSED
275531	60/109,607	November 23, 1998	LAPSED
275820	60/134,848	May 19, 1999	LAPSED
275980	60/148,288	August 11, 1999	LAPSED
275842	60/185,390	February 28, 2000	LAPSED
276451	60/189,050	March 14, 2000	LAPSED
275675	60/193,467	March 31, 2000	LAPSED
275477	60/199,365	April 25, 2000	LAPSED
275545	60/209,584	June 6, 2000	LAPSED
275474	60/210,451	June 9, 2000	LAPSED
275490	60/212,668	June 20, 2000	LAPSED
275819	60/213,252	June 22, 2000	LAPSED
275471	60/217,706	July 12, 2000	LAPSED
275435	60/233,607	September 18, 2000	LAPSED
275544	60/233,625	September 18, 2000	LAPSED
275473	60/241,022	October 20, 2000	LAPSED
276519	60/257,147	December 22, 2000	LAPSED
277109	60/264,318	January 29, 2001	LAPSED
280060	60/280,139	April 2, 2001	LAPSED
280616	60/300,063	June 25, 2001	LAPSED
277149	60/303,813	July 10, 2001	LAPSED
282445	60/331,187	November 9, 2001	LAPSED
279155	60/331,481	November 16, 2001	LAPSED
280678	60/341,858	December 21, 2001	LAPSED
280677	60/341,860	December 21, 2001	LAPSED
280703	60/357,140	February 19, 2002	LAPSED
280692	60/367,727	March 28, 2002	LAPSED
280750	60/381,328	May 20, 2002	LAPSED

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Matter No.	Serial No.	Filing Date	Status
280757	60/386,746	June 10, 2002	LAPSED
280759	60/386,747	June 10, 2002	LAPSED
280761	60/386,748	June 10, 2002	LAPSED
280760	60/386,759	June 10, 2002	LAPSED
280724	60/390,191	June 21, 2002	LAPSED
280763	60/396,082	July 17, 2002	LAPSED
280767	60/396,141	July 17, 2002	LAPSED
280764	60/396,255	July 17, 2002	LAPSED
280758	60/400,687	August 5, 2002	LAPSED
280772	60/405,318	August 23, 2002	LAPSED
280773	60/405,319	August 23, 2002	LAPSED
280765	60/410,506	September 13, 2002	LAPSED
291922	60/427,564	November 20, 2002	LAPSED
291923	60/428,274	November 22, 2002	LAPSED
291918	60/452,928	March 10, 2003	LAPSED
277113	09/238,741	January 28, 1999	PENDING
275818	09/259,337	March 1, 1999	PENDING
275984	09/259,338	March 1, 1999	PENDING
275478	09/435,992	November 8, 1999	PENDING
275532	09/447,594	November 23, 1999	PENDING
275681	09/576,424	May 22, 2000	PENDING
275543	09/612,914	July 10, 2000	PENDING
280721	09/628,186	July 28, 2000	PENDING
275726	09/635,929	August 10, 2000	PENDING
276603	09/758,173	January 12, 2001	PENDING
276658	09/772,938	January 31, 2001	PENDING
277869	09/791,551	February 26, 2001	PENDING
277931	09/798,525	February 21, 2001	PENDING
279190	09/805,217	March 14, 2001	PENDING
280062	09/822,672	April 2, 2001	PENDING
280609	09/840,872	April 25, 2001	PENDING
280618	09/853,580	May 14, 2001	PENDING
280617	09/853,581	May 14, 2001	PENDING
280623	09/855,717	May 16, 2001	PENDING
280624	09/856,534	September 4, 2001	PENDING
280632	09/874,141	June 6, 2001	PENDING
280637	09/883,962	June 20, 2001	PENDING
280657	09/954,274	September 18, 2001	PENDING
280728	09/982,849	October 22, 2001	PENDING
280731	09/985,646	November 5, 2001	PENDING
280732	09/986,174	November 7, 2001	PENDING
280727	10/058,069	January 29, 2002	PENDING
280743	10/058,120	January 29, 2002	PENDING
280705	10/073,138	February 13, 2002	PENDING
280745	10/096,963	March 14, 2002	PENDING

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Matter No.	Serial No.	Filing Date	Status
280747	10/109,853	April 1, 2002	PENDING
280748	10/113,929	April 2, 2002	PENDING
280749	10/171,680	June 17, 2002	PENDING
280752	10/171,681	June 17, 2002	PENDING
291568	10/191,052	July 10, 2002	PENDING
280766	10/195,426	July 16, 2002	PENDING
280771	10/211,357	August 5, 2002	PENDING
291806	10/241,832	September 12, 2002	PENDING
291807	10/241,836	September 12, 2002	PENDING
291872	10/291,532	November 12, 2002	PENDING
291921	10/295,823	November 18, 2002	PENDING
301015	10/326,924	December 23, 2002	PENDING
301988	10/367,978	February 19, 2003	PENDING
302468	10/384,356	March 10, 2003	PENDING
305940	10/661,086	September 12, 2003	PENDING
307430	10/743,398	December 23, 2003	PENDING
307368	10/743,739	December 24, 2003	PENDING
276000	60/148,287	August 11, 1999	PENDING
304387	60/479,910	June 20, 2003	PENDING
306302	60/510,552	October 14, 2003	PENDING
306645	10/703,669	November 10, 2003	PENDING
308678	10/796,158	March 10, 2004	PENDING
310260	10/871,261	June 21, 2004	PENDING

Attorney Docket: 037003-0280705

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:
Anderson *et al.*

Confirmation Number: 7969

Application No.: 10/073,138

Group Art Unit: 1644

Filed: February 13, 2002

Examiner: Phillip Gambel

Title: Identification of Unique Binding Interactions Between Certain Antibodies and the Human B7.1 and B7.2 Co-Stimulatory Antigens

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mitchell Reff, Ph.D., do hereby declare and state as follows:

1. I am presently Vice President of Discovery Oncology at Biogen Idec Inc. and a co-inventor of the present application. I have been employed by Idec Pharmaceuticals Corporation, now Biogen Idec Inc. since 5/21/90 (insert date). I was actively working on the subject matter of the present application prior to and upon filing of the application in the USPTO. Based upon the foregoing, I am in a position to attest to the following fact.

2. The following sequence errors were noted in the original nucleotide and amino acid sequence for the 16C10 (heavy and light chain) and 7C10 (heavy chain) antibodies in the Amendment Under 37 C.F.R. §1.111 filed on August 28, 2005. Nucleotide position 58 of SEQ ID NO: 2 (the heavy chain 7C10 nucleotide and amino acid sequence) as originally filed disclosed a guanine (g), while the corresponding amino acid at position 20 disclosed a glutamate (Glu). Nucleotide position 68 of SEQ ID NO: 5 (the light chain 16C10 nucleotide and amino acid sequence) as originally filed disclosed a thymine (t), while the corresponding amino acid sequence at position 23 disclosed a valine (Val). Nucleotide position 412 of SEQ ID NO: 5 disclosed a thymine (t), while the corresponding amino acid sequence at position

138 was a serine (Ser). Nucleotide position 523 of SEQ ID NO: 6 (the heavy chain 16C10 nucleotide and amino acid sequence) as originally filed disclosed a cytosine (c), while the corresponding amino acid sequence at position 175 was leucine (Leu).

3. The substitute sequence listing filed August 28, 2005 amended SEQ ID NOS: 2; 5, and 6. Specifically, the guanine at position 58 of SEQ ID NO:2 was corrected to a cytosine (c), thus changing the corresponding amino acid from a glutamate (Glu) to a glutamine (Gln). The thymine at position 68 of SEQ ID NO: 5 was corrected to a cysteine (c), thus changing the corresponding amino acid from a valine (Val) (gtc) to an alanine (Ala) (gcc). The thymine at position 412 of SEQ ID NO: 5 was corrected to adenine (a) thereby changing the corresponding amino acid from a serine (Ser) to a threonine (Thr). The cytosine at position 523 of SEQ ID NO: 6 was corrected to a guanine (g), thus changing the corresponding amino acid from a leucine (Leu) to a valine (Val).

4. Figure 5A of the application displays the nucleotide and amino acid sequence for the 16C10 light chain antibody. The following errors in the originally filed Figure 5A were noted in the Amendment Under 37 C.F.R.§1.111 filed on August 28, 2005. Nucleotide position 68 of original Figure 5A disclosed a thymine ("t"). Nucleotide position 412 of Figure 5A disclosed a thymine ("t"). Original Figure 5A displayed a valine (V) at amino acid sequence position 23, and a serine (S) at amino acid position 138. These were inadvertent errors.

5. The replacement Figure 5A, filed on August 28, 2005, amended originally filed Figure 5A. Specifically, the thymine at nucleotide position 68 was corrected to a cysteine (c), and the corresponding amino acid at amino acid position 23 was corrected from a valine (V) to an alanine (A). The thymine at position 412 was corrected to an adenine (a), and the corresponding amino acid at position 138 was corrected from a serine (S) to a threonine (T).

6. I declare that the amendment to the nucleotide and amino acid sequence of the 16C10 heavy chain antibody as described in paragraphs 2 and 3 above, now teach the correct sequence for the 16C10 heavy chain nucleotide and amino acid sequence specifically identified in Figure 5B of the application as originally filed.

7. I declare that the amendment to the nucleotide and amino acid sequence of the 7C10 heavy chain antibody as described in paragraphs 2 and 3 above, now teach the correct

sequence for the 7C10 heavy chain nucleotide and amino acid sequence specifically identified in Figure 3B of the application as originally filed.

8. I declare that the amendment to the nucleotide and amino acid sequence of the 16C10 light chain antibody as described in paragraphs 2 and 3 above, now teach the correct nucleotide and amino acid sequences for the 16C10 light chain antibody specifically identified in the application as originally filed.

9. I further declare that hybridoma HB-12119 of the American Type Culture Collection (ATCC) produces the 16C10 antibody and was received by the ATCC depository May 29, 1996. The nucleotide sequence encoding the 16C10 antibody produced by hybridoma ATCC accession number HB-12119 corresponds to the corrected nucleotide sequence as set forth in amended SEQ ID NO: 5. The nucleotide sequence set forth in amended SEQ ID NO: 5 encodes the amino acid sequence set forth in SEQ ID NO: 5. In addition, the 16C10 nucleotide and amino acid sequences expressed by hybridoma ATCC accession number HB-12119 corresponds to the nucleotide and amino acid sequences in replacement Figure 5A. Accordingly, the substitute nucleotide and amino acid sequence listing (SEQ ID NO: 5) for the 16C10 light chain antibody does not constitute new matter because these sequences are the correct sequences for the 16C10 light chain antibody specifically identified in the originally filed application as expressed by hybridoma (HB-12119).

10. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and believe are believed to be true, and that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issued thereon.

5/11/06

Date

Mitchell Reff, Ph.D.